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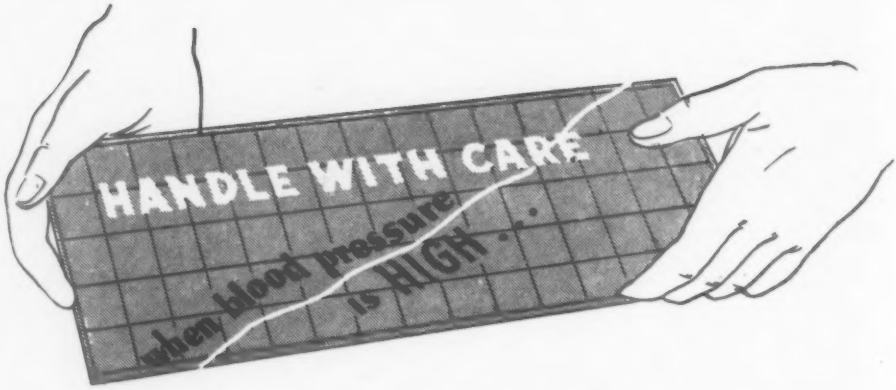

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THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

DECEMBER, 1943

ORIGINAL ARTICLES

GRADENIGO SYNDROME COMPLICATED BY PNEUMOCOCCIC MENINGITIS; RECOVERY AFTER INTENSIVE TREATMENT WITH PENICILLIN AND SULFADIAZINE

By Lewellys F. Barker, M.D.*
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(From the Medical Clinic of the Johns Hopkins Hospital)

Though the Gradenigo syndrome (otitis media with head pains and paralysis of the 6th nerve on the same side) is less rare than was formerly thought, the case reported here is of especial interest because of the pneumococcic meningitis that developed and the favorable outcome under intensive treatment with penicillin and sulfadiazine.

Case History. The patient, a white woman, aged 35, an inspector in a manufacturing plant, entered the medical service of the Johns Hopkins Hospital on January 8, 1943, in a state of coma.

Family History. Has no bearing on the case.

Previous History. Aside from the ordinary diseases of childhood the patient has had fairly good general health. She suffered from several attacks of tonsillitis and 6 years ago had her tonsils and adenoids removed. She has had occasional headache and wears glasses for reading. Her habits have been good and she has worked steadily at her occupation until the present illness.

Present Illness. Two weeks before admission the patient developed a cold with sore throat and occasional stopping up of the ears. On January 2, on returning from work, the right ear ached. She developed general malaise and headache and was given drops to put into her ears by a local physician. At night she began to vomit, developed fever and had a chill. The next day she remained in bed but at night became delirious and her local physician finding a temperature of 105.5° F. gave her sulfathiazole, 1 gm. every 2 hours. Owing to persistent vomiting not much of the drug was retained and the medication was stopped. The vomiting persisted, the patient remained in a semidelirious state, and on January 6 was taken to the South Baltimore General Hospital. The temperature was then 105° F. and on account of the persistent delirium lumbar puncture was done and the cerebrospinal fluid was found to be cloudy and to contain 3300 cells, P.M.N. predominating. She was then sent to the Johns Hopkins Hospital for treatment of the meningitis and for further study.

Physical Examination on Admission. Temperature, 104.4° F.; pulse rate, 116; respiratory rate, 24; blood pressure: 120 systolic, 75 diastolic. Well-developed and well-nourished. Semicomatose but responds to painful stimuli. Skin dry. Face flushed. Breathing stertorous. Right eyelid swollen and red with yellow pus on conjunctiva. On moving the head the eyes remain fixed. Pupils small, equal, react to light. Right optic disk slightly hazy and veins

* Dr. Barker died July 13, 1943, a few months after submitting this manuscript.

rather full. Left optic disk normal. Right aural canal inflamed; drum injected and bulging. Pressure over the right mastoid causes pain. Purulent exudate in nose. Herpes on right cheek and on left upper lip. Heart and lungs negative. Abdomen negative. Bladder partially distended. Neck rigid on forward flexion and on rotation. Kernig sign bilaterally positive. Brudzinski positive. Other reflexes negative.

Laboratory Tests. Blood on admission showed a leukocytosis (white count, 20,200). Urine contained albumin on admission but soon became normal.

An ear, nose and throat consultant found pus draining from sphenoids, ethmoids and both antra.

Examination of the spinal fluid sent from the South Baltimore General Hospital revealed pneumococci within the pus cells.

On the following day there was complete paralysis of the right nervus abducens and beginning paralysis of the right nervus facialis.

Diagnosis. Purulent sinusitis with extension along the right Eustachian tube to the ear causing right otitis media, right mastoiditis and right petrositis with the development of pneumococcus meningitis and paralysis of the 6th and 7th cerebral nerves.

Treatment and Further Course. At 1.30 A.M. on January 7, 20,000 units of sodium penicillin (Florey) were given intravenously. At 2.15 A.M. lumbar puncture was repeated, 3040 white cells found, 94% polymorphonuclears, and 5000 units of penicillin were given intrathecally.

The culture that had been made on the preceding day from the spinal fluid showed a pure growth of pneumococci, Type 25, and a blood culture made on January 7 also revealed Type 25 pneumococcus.

At 3.30 A.M. on January 7, 15,000 more units of penicillin were given intravenously. Roentgen ray of the skull made on this day showed no evidence of destruction within the mastoid, but at 4.30 A.M., 1500 cc. salt solution and 500 cc. of 5% glucose were given intravenously and myringotomy and simple mastoidectomy on the right were performed. The mastoid was found to be markedly infected and was necrotic.

At 6.00 A.M., ½ hour after the completion of the operation, 15,000 units of sodium penicillin were given intravenously and the same amount at 7.30 A.M. and at 9.30 A.M.

At noon on January 7, 6 gm. of sodium sulfadiazine were given intravenously along with 500 cc. of citrated blood. The patient continued to look gravely ill, the eyes were fixed and directed toward the left. Another lumbar puncture was done at 5.00 P.M. on that day. The white cell count in the cerebrospinal fluid had already decreased to 6400 and culture made from the fluid on this day and from the vein remained sterile. The sulfadiazine level in the blood on January 7 was 17.6 mg. per 100 cc. At 8 P.M. on that day 3 gm. of sodium sulfadiazine were given intravenously along with saline and 5% glucose solution. On January 8 at 1 P.M., 5000 units of sodium penicillin were given intrathecally and 2 gm. of sodium sulfadiazine along with 5% glucose and saline were given intravenously. The sulfadiazine level in the blood was 11.6 mg. per 100 cc. There was a lessening of the depth of the coma, complete 6th nerve paralysis on the right and some weakness of the right facial nerve. Facial herpes continued as did the rigidity of the neck and the positive Kernig sign.

At 11 P.M. on January 8, 5000 units of sodium penicillin were given intrathecally and 2 gm. of sodium sulfadiazine intravenously. An hour later, 5000 units of sodium penicillin were given intrathecally.

On January 9, the white count in the cerebrospinal fluid was 7480; 5000 units of sodium penicillin were given intrathecally.

The patient began to improve rapidly, the temperature fell, she recognized people and talked with them but had occasional delirium. On this day a total of 8 gm. of sulfadiazine were given intravenously in divided doses.

On January 10, the temperature had become normal and the patient talked rationally. Six gm. of sodium sulfadiazine were given by clysis.

On January 11, 5000 units of sodium penicillin were given intrathecally and the sulfadiazine level in the blood was 6.2 mg. per 100 cc.

The right facial paralysis had become more marked and the paralysis of the right nervus abducens persisted.

On January 13, the patient complained of diplopia owing to the persistence of the right abducens paralysis.

Thereafter the patient continued to do well except for the persistence of paralysis of the nervus abducens and of the nervus facialis on the right. The penicillin and sulfadiazine were discontinued. It seems probable that the patient will recover later from the paralyses of the nerves.

Comment. The patient has been very fortunate in making such a good recovery from a pneumococcus meningitis. Until recently this disease has almost always proved fatal, though with the advent of the sulfonamide drugs many patients have recovered. In this case both penicillin and sulfadiazine were given in very large doses. In how far to attribute the recovery to penicillin, on the one hand, or to sulfadiazine on the other, or to both, is anyone's guess. Penicillin is known to have remarkable antibacterial powers against Gram-positive bacteria. Sulfadiazine is the safest of the sulfonamide drugs and it is unfortunate for the civilian population that temporarily the U. S. Army has had to take up so much of the supply that civilian hospitals for the present are asked to use other sulfonamide preparations as far as possible.

THE FEVER CURVE OF THERAPEUTIC FADS*

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It is, of course, all important that new therapies should be discovered, introduced into medical practice, and evaluated by actual use, for only in this way will the treatment of disease improve. However, it is unfortunate that almost every new therapy seems to have to suffer a similar fate at the hands of the medical profession. Each seems to have to run the gamut of overenthusiasm, disillusionment and neglect. Such a course of events appears at present to be inherent and inevitable.

One might draw a graph of the progress of a therapeutic fad just as one plots the fever curve of an infectious disease. The course of the graph will, in many instances, prove to be characteristic and recognizable, just as medical science has become familiar with the typical course of many fevers and can, from the fever curve, diagnose not only the morbid entity but the stage of the disease and sometimes deduce something of the prognosis.

Typhoid fever is the classical example of a disease with a characteristic fever curve, familiar, from extensive experience, to all but the youngest doctors. Three phases are recognized in the fever curve of typhoid—the stage of invasion with its daily rise to a higher evening

* Address to the Undergraduate Medical Association, May 26, 1943.

peak; secondly, the high maintained fever of the fully established disease, the fastigium; then when all goes well the fever commences to oscillate as the so-called amphibolic stage is reached. Finally, the falling curve of defervescence drops below normal for the first weeks of convalescence until all is restored to normal physiologic health.

When a newly recognized disease is defined it takes much study and many observations to enable us to know its typical course and symptoms. Once learned, however, we can make use of this information about the new just as we do in our old enemy typhoid fever. Could we perhaps think of a therapeutic fad as an epidemic infectious disease; could we by studying its course and behavior learn enough of its fever curve to diagnose it early, to recognize its state and even to prophesy its future? If we could do this we might be less readily swept away by each new fad; we might avoid the complications and dangers which are likely at the height of the fever; we might escape the later disappointment and remorse which should be the punishment for our loss of common sense and critical judgment. Although it may be stated parenthetically, such remorse does not seem to weigh very heavily on most of us; once the fad is dead, its evils are forgotten. This is fortunate for the physician's peace of mind but not for his scientific growth nor for his future patients.

An infectious disease picture is the result of interactions between the causative agent and the host. A therapeutic fad is equally so. There must occur a period of invasion after the introduction of a new therapy during which occur prodromata in the form of reactions of interest displayed by the host. After a varying period the actual onset of the fad takes place with rapid spread in the use of the new medicament and a feverish interest in it. Soon the disease is at its height. The symptoms, in a classical instance, include at this stage an unwarranted enthusiasm for the curative effects of the new drug or treatment, an extension of its use for all sorts and kinds of ailments quite foreign to the claims of the original discoverer. Soon a delirious euphoria develops which sees the new therapy as a panacea for all ills. At this stage, the mind and reasoning power of the profession seem to be obtunded.

One factor which raises the fever of the fad to even higher levels is the publication of reports of remarkable therapeutic results claimed for the method. Unfortunately, these reports are frequently hasty and ill-considered. The authors often are honest but deceived in their enthusiasm, attributing to the therapy of the moment benefits which may, in fact, be due to the psychotherapeutic influence of this same enthusiasm, or to associated items of treatment such as rest and diet. Where everything is being done for a patient, it is risky to give credit to any one procedure. One must be careful not to fall into the common error of "post hoc ergo propter hoc" reasoning. Improvement after a certain treatment does not always justify an assumption of therapeutic relationship.

Neither the fever of typhoid nor the frenzy of the fad ends by crisis. The maintained height of the curve is broken by increasingly sharp

falls with slowly returning consciousness and common sense. Reports of therapeutic failures and of toxic effects begin to appear. Criticisms of the method multiply until finally the good results obtained in certain cases are lost sight of and forgotten. It is not appreciated that the successes occurred only in properly selected cases, the failures in all others, for at this stage the criteria for proper selection are not clear. Unjustly, therefore, we turn against the method altogether, we forget its real value and discard it completely. The fever is now "broken," it is below normal and the disease is over. Convalescence is slow. After a kind of negative phase of complete inactivity, interest slowly returns through some reappraisal of evidence or improvement in method. And final restoration of health is reached when only a proper and judicious use is made of what was once a frenzied fad.

This may all sound fanciful and forced but the history of medicine records innumerable instances of therapies which have run just such a fever curve. And anyone who has lived some years in medicine has seen such incidents and has probably experienced it himself although it may be difficult for him to believe that he was ever so deluded. Let us choose a few examples.

Venesection is, of course, the most familiar example. Used without clear indications throughout the middle ages, its abuse came to a height with Benjamin Rush and the epidemics of yellow fever in Philadelphia toward the end of the 18th century. That any of his patients recovered amazes us today, as we read of the repeated large bleedings to which they were subjected.

When the pulse "acts with force" 10 to 20 ounces were removed; when the pulse was weak it was better to take only a few ounces at a time, repeating the process 3 or 4 times a day. But "if the state of the pulse be our guide, the continuance of its inflammatory action, after the loss of even 100 ounces of blood, indicates the necessity of more bleeding, as much as it did the first time a vein was opened."

And yet it all seemed so logical to Rush! As the blood settled in the bleeding bowl a buffy coat or, as it was called, "size" was formed. When this was thick it was sure evidence of noxious matter in the blood and, therefore, a clear indication for further bleeding. Today we know that this increased "size" of the blood was due to rapid sedimentation of the red cells as seen especially in infections, pregnancy and anemia. It was accordingly in infectious diseases and pregnancy that the fad of venesection rose to its greatest heights. Also it is obvious to us that the more one bled the more anemic the blood, the more rapid the sedimentation, the thicker the buffy coat and the clearer the indication for further bleeding. To quote Rush himself—"Bleeding should be repeated while the symptoms which first indicated it continue, should it be until four-fifths of the blood contained in the body are drawn away." What a logical but tragic vicious circle! It took a century before venesection recovered from these unwise excesses; the indications for venesection had to be reappraised before the method found its proper level of usefulness.

Benjamin Rush may seem so long ago that one may ask whether this century has seen any such therapeutic fads. The answer is a strong affirmative. For example, on the completion of my internship in 1910, I started to work in the Medical Outpatient Department of the University Hospital. My chief was an enthusiastic believer in the virtues of Thiosinamine. The fact that you have never heard of this drug does not alter the fact that in 1913 the Index Catalogue of the Library of the Surgeon General's Office, U. S. Army, recorded 76 articles and 4 books on the therapeutic uses of thiosinamine. It was believed to relax scar tissue wheresoever it might be; it was especially useful in stricture of the esophagus and in mitral stenosis. Many the case of rheumatic carditis I was made to listen to in order to record the improvement as the drug relaxed the stenotic mitral ring. As I think back to those days and develop my thesis in this essay, I almost find myself wondering whether there might not be some grain of value in this long neglected drug.

All the fads, however, have not been on the medical side of the house. The past half century has seen a number of surgical procedures, for what one might term neurasthenia, be introduced, rise to popularity and be abandoned as useless. Two of these, nephropexy and gastropexy, seemed at least to find some justification in the easily demonstrable ptotic position of the respective organs. Unfortunately, the logic that the nervous state was the result of the ptosis and would be benefited by restoring the fallen organ to its normal position was wholly fallacious.

The cart was far in front of the horse, for as we now know the primary trouble is the relaxed nervous tone of the patient and the ptosis of the abdominal viscera is but one manifestation of this, and certainly not the causative factor. Many have demonstrated that the position of the stomach in such individuals varies in both directions with the level of vasomotor and nervous tone. It is hard to believe in retrospect, how sure we all were of the good results of this useless surgery, and it is amazing how difficult it is to forget such useless knowledge as the technique of gastropexy which was much emphasized by prominent teachers to us medical students of those days. Of course, it is obvious that everyone was carried away by the apparent reasonableness of the procedure and was self-deceived by the not infrequent temporary benefits due in all probability to the psychotherapeutic effect of the operation. Any similarly spectacular treatment might have done as well. Like all such fads this one ran its course and was abandoned. But as always, another was ready to take its place.

One of the most virulent attacks from which the profession has suffered, not to mention the thousands of patients, was the fad of intestinal autointoxication. This was no single frenzy for it resulted in many secondary or complicating troubles. It again seemed so logical and reasonable; toxic matters must be formed in the gut, their absorption must obviously cause any or all symptoms. The degree and kind of this process could be estimated by the degree and exact tint of the

indican reaction in the urine—light or dark green, blue or bluish green. From this start, the fad followed obvious roads leading to the absurdities of "high colonics" carried out in cubicled offices resembling stables with many stalls. When this field began to fail, these cells were found equally convenient for the similar nonsense of duodenal lavage. The same honest but self-hypnotized physicians, often the same patients—the only change the tube and the orifice.

At least these results of the autointoxication theory were relatively harmless, but the fever had to rise to higher levels. If the colon was the site of this production and absorption of toxic matters, what more sensible than to remove the offending part? Incredible as it sounds today, this was advocated and done by not a few leaders of the profession, sometimes with a high operative mortality. This fad is now as dead as some of its victims. One may say that medical science must advance by trial and error—but in this case the error seems to have been on the inexcusable side.

Sometimes a therapy, medical or surgical, remains improperly thrown into the discard because at the time it is not possible to discover the correct indications for its use. In this situation is Edebohl's operation of decapsulation of the kidney. First introduced for so-called "nephralgia," it was later used more logically to relieve tension within the renal capsule in the hope of obtaining diuresis in cases of anuria and nephrosis. The results were occasionally spectacular, but far more often no benefit was obtained. It may yet be revived as a method of cutting the sympathetic nerve supply to the kidney in cases of hypertension.

In such a situation the probable explanation is that this particular operation should only be performed in one selected group of cases, which we as yet cannot distinguish from the larger group. This is what is happening today to the surgical treatment of hypertension. We have seen the therapy introduced, have read many glowing reports of cures and are now in the stage of being disillusioned by frequent failures. It looks today as if the therapy was about to be dropped by all but the die-hard enthusiasts. There is no doubt whatever that in a very few patients the method gives remarkable relief. But in which patients? How does one select them? It is not enough to say that they must be in condition to withstand the surgery, we must learn to divide the cases of hypertension into their different etiologic classifications. Then and then only, will we be in a position to select those who will respond to surgery. We cannot expect a surgical operation to cure all patients with what in the final analysis is only a symptom and one which results from more than one cause.

These are perhaps enough examples from the past—but it would be easy to mention others such as the tonsillectomy craze which at one time, not so long ago either, approached the violence of the Dancing Mania of the Middle Ages. Even today the now well-established indications for removal of tonsils are not always respected. Dental extractions are also finding their proper indications but the removal of

impacted molars, merely because they are impacted, or the patient anemic or neurasthenic, still goes on merrily. In all such situations the great need is a clarification of the therapeutic indications, the great danger that lacking such proper control of its use it will cause disappointment, be considered useless thus denying its help to the few whom it would benefit.

Was there really no virtue in strychnine in spite of the tons prescribed by honest physicians to the depressed, the asthenic and the convalescent? Does calomel deserve its present oblivion? Therapeutic nihilism comes from repeated disillusionment. To avoid this, we must try to diagnose our current fads, to recognize the misuse of new therapies in time to prevent the excesses which lead to disappointment and discard. Let us look at the therapies of today with a critical eye.

It is safe to assume that at almost any given moment the medical profession has just recovered from one fad, is suffering actively from another and that still a third is incubating. Can we possibly see ourselves sufficiently clearly to recognize these? What stage of the vitamin fad are we in today? It must certainly be at its height for it would seem impossible for more patients to take more vitamins than is the case now. We must be approaching the end of the fastigium and soon will see the fevered excesses cease and the use of vitamins tend to be neglected until placed on a reasonable basis.

Advertising of vitamins must also, it would seem, be at its apogee. Commercial advertising cannot be blamed for the therapeutic fads of the medical profession but it is surely a contributing factor, just as the delirium of fever will be more violent in those much addicted to alcohol. Let us not allow ourselves to become too subject to the influence of alcohol or of advertising, however honest, lest we reap the whirlwind in our next fever or fad. Advertising and alcohol are both excellent things within reason.

What of the sulfonamides? It seems inconceivable that any of our enthusiasm for these medicaments will ever be looked back on as a fad. The evidence is too conclusive, the logic is so sure. And yet were we not just as sure of our facts in the period when we cured meningeal infection with the formaldehyde given off in the spinal fluid by administered urotropin? Read the literature on the treatment of septicemia and puerperal sepsis by intravenous mercurochrome. The problem was solved and yet the method fell into disrepute long before sulfanilamide was available.

As usual we feel sure of our ground with regard to the sulfonamides. We believe we know something of the mechanism by which this series of substances act in bacterial infections and as usual everything is logical. But now we are being led to believe that the sulfonamides are equally curative in certain virus diseases. Does what we know of the viruses make it probable that the antibacterial mechanism of the sulfonamides would also be antiviral? If not, can it be that we are at the old game of deceiving ourselves—impossible, of course—as usual?

At any rate we must admit we are going too far in our administration of the sulfonamides. Fever is, for many, a sufficient indication for a trial of some sulfonamide, and yet the sulfonamides cause fever and we are off on a vicious circle not so different from that followed by Rush. Because sulfonamides act in some infections they are tried in all infections—especially today in the virus pneumonias to the discomfort of the patient and the waste of not too abundant sulfonamide.

We have reached the stage at which reports of toxic effects and therapeutic failures are appearing in the medical press. We need not here review the toxic manifestations but some are serious and even fatal, nor the causes for failure other than the sulfonamide-resistant strains of pneumococci and even gonococci. Warnings against the promiscuous use of sulfonamides are now appearing. It seems impossible, of course, that any of these factors should ever swing the pendulum to a neglect of the obvious value of these chemical drugs—yet let us not be too complacent—there is many a precedent for behavior almost as absurd.

We have touched on a few of the therapeutic fads of the past; we have cast a bilious eye on the fads of the present—but what new fad is incubating prepared to start us on some feverish episode? Perhaps it will be still another anti-bacterial derived from moulds, perhaps an almost instantaneous cure of syphilis or even of all venereal diseases, or shall we all be breathing triethylene glycol many hours a day—even wearing masks to enable us to do so when we are out in the dangerous fresh air. Prophecy is always difficult and, with regard to fads, impossible.

The most we can do is to be on the alert to recognize the next in its incipiency. We must diagnose it early from its characteristic symptoms and course.

We must keep a watch upon ourselves constantly lest we follow the same roads that we have before. We must be critical and even skeptical without losing our optimism or our openmindedness. We must scrutinize our therapeutic achievements to be certain they are surely due to the therapy we praise and not to insidious subtle psychotherapeutic effects unintended and unsuspected by ourselves. We must be sure our good results are not due to good associated care, diet and rest, or even to that very real force the "vis medicatrix naturae." If we are sure of the action of a therapy we must remember that it will be specific or of benefit, only in certain cases and we must not be led to try it in all. Let us try to judge matters for ourselves and not merely follow the herd blindly.

Finally, let us admit that we are human and have all the frailties of our predecessors and contemporaries in medicine. If we start with this premise we shall come more humbly to a self-correcting realization of our own lack of resistance to therapeutic fads. None of us is immune—but if we can recognize the danger we can perhaps avoid the contagion.

THE DETRIMENTAL EFFECT OF FREQUENT TRANSFUSIONS IN THE TREATMENT OF A PATIENT WITH HEMOPHILIA

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(From The Charlotte Drake Cardeza Foundation, Division of Hematology, Jefferson Medical College and Hospital)

Many agents have been recommended for the treatment of hemophilia, but with one exception they have not stood the test of time. This exception is transfusion of blood. Most discussions of the treatment of hemophilia agree that a transfusion of normal blood, plasma, or fractions prepared from plasma[2–6] results in a definite though transient improvement in the condition, usually lasting 2 to 6 days.

Until recently the technique of blood transfusion was sufficiently complicated to restrict its use in hemophilia to acute manifestations of the disease. The availability of this form of therapy has greatly increased in the past few years because of the development of blood banks. It has, therefore, become feasible to use transfusions as a therapeutic agent much more frequently, without restricting their use to emergencies as previously.

So far there has been no indication that the use of frequent transfusions in treating hemophiliacs is contraindicated in any way. Observations which we have made on one case of hemophilia indicate, however, that both from a clinical standpoint, and from the aspect of clotting time, repeated transfusions of either whole blood or plasma lose their effectiveness in alleviating the condition, and even possibly have a detrimental effect. These observations extend over a period of about 4 years during which the patient received at least 3000 cc. of whole blood and 5000 cc. of plasma. The plasma used was in various forms, either prepared from freshly drawn blood, from 4-day old bank blood, or from lyophilized plasma restored to its original volume. During the latter part of this period detailed records were kept on the blood coagulation time and clinical condition of the patient, but for the earlier part detailed records are missing.

The patient under discussion is a hemophiliac, aged 36, with a family history of the maternal grandfather and second cousin both manifesting the disease. His history follows the usual course of hemophilia in a moderately severe form. He has had hemorrhages into various joints with resulting ankylosis of both elbows, the left knee and the right ankle. On frequent occasions since the age of 18 he has had hematuria due to hemorrhages originating in the kidneys.

The period covered by this report commenced in August, 1939, when he was admitted to the hospital due to a hemorrhage in the left thigh compressing the sciatic nerve. At this same time a severe hema-

turia developed and a transfusion of 500 cc. of citrated blood was given. This failed to stop the hematuria and was followed by transfusions on 3 successive days of 50 cc. of plasma. Following this the hematuria stopped.

At that time it was decided to obtain a quantity of normal plasma and preserve it in the lyophile state for therapeutic use. Approximately 450 cc. of plasma were lyophilized in 25 cc. lots. As the need arose, indicated by the appearance of hemorrhages, 1 or 2 of the vacuoles were restored to the original volume and injected intravenously. During the year that this supply of dried plasma was available it was given on the average of once a month. While no record of blood coagulation times were kept, it was observed that the plasma initially had beneficial effects, but that later its effectiveness decreased.

After the supply of lyophile plasma was exhausted, no transfusions of any kind were given for a period of about 6 months. At this time (March, 1941) the patient's clinical condition became very poor and the plasma from about 75 cc. of fresh blood was given. A marked improvement resulted and the patient was free from hemorrhagic symptoms for a period of about 3 weeks. The beneficial effect was so marked that on the reappearance of hemorrhages another transfusion of fresh plasma was given; this time, however, no improvement of his condition occurred. Further attempts to ameliorate his condition by transfusions of 50 to 100 cc. of fresh plasma given at intervals of 2 to 3 weeks also produced no result.

In August, 1941, the patient came under our care, and it was decided to conduct a further study of the effect of transfusions on his condition. The record of the transfusions given is shown in Table 1 together with the clotting times of venous blood taken before and after the transfusions. Since the patient's red blood cell level was usually normal, in some cases 500 cc. of blood were withdrawn before giving the transfusion. As shown in the table, none of these transfusions had any effect on the clotting time with the exception of those given on 9–10–41 and 11–28–42. It is also noteworthy that the clotting time has had a tendency to increase during this period. Clinically, the condition of this patient has become somewhat worse. It has been noted particularly that while he previously had severe phases alternating with periods of relative remission, he now appears to be in a continuous severe phase which has persisted for about a year.

Discussion. The observations presented here indicate that in one hemophiliac who has received numerous transfusions during the past 3 years the beneficial effect of transfusions has become questionable and even suggest that they may have become detrimental. We feel that in view of these observations, care should be taken in treating hemophiliacs by transfusions, and that they probably should not be given them as a prophylactic measure but, rather, that the measure be reserved to cope with emergencies. Johnson[3] has reported on the successful prophylactic treatment of two hemophiliacs by transfusion of lyophile plasma over periods of 3 and 5 months respectively. This, however, is not comparable to the period of 3 years during which this

patient has been treated, and it may well be that with continued treatment his patients will also develop a refractory phase.

TABLE 1.—RECORD OF TRANSFUSIONS AND CLOTTING TIMES

Date 1941	Transfusions: Whole blood (cc.)	Transfusions: Plasma (cc.)	Blood removed (cc.)	Clotting time of venous blood: Before transfusion Hr.	Before transfusion Min.	After transfusion Hr.	After transfusion Min.
8–14	..	250	..	3	45	1	00
8–26	..	250					
8–27	..	250	..	..	..	2	50
8–28	..	200	..	..	..	3	25
9–10	..	250	..	3	00	0	30
9–11	..	250	500	2	00	2	30
9–23	..	300	500	2	50	1	35
9–26	..	200					
9–30	..	350	500	3	30	2	30
10– 3	..	300	..	3	30	2	20
10– 8	500						
11– 3	120	..	..	2	30	2	00
12–30	..	..	500				
1942							
1– 8	..	..	..	2	15		
3–11	500	..	..	4	45	3	20
3–13	500	..	500	8	30		
3–20	..	250					
3–25	500	..	..	7+	..	4+	
6– 4	..	..	500				
7–20	..	..	500				
7–21	..	250					
8–14	..	200					
9– 5	..	275					
10–22	..	..	500				
11–21	500	..	500				
11–28	..	300	..	4	00	0	40
12–24	..	300					
1943							
2– 1	..	300	..	6	00	5	30
2– 3	..	300	..	5	00	4	30

Certain *in vitro* experiments, which were made with this patient's blood during this refractory phase, suggest a possible explanation as to its cause. It is commonly accepted that the addition *in vitro* of a small quantity of normal blood to hemophilic blood produces a normal clotting.[1,2,5] Previous to the period discussed in this paper it had been frequently observed that this was the case in respect to the blood of this patient. In 1941, following the series of 8 plasma transfusions totaling 1800 cc., this phenomenon was studied again on this patient, using plasma from oxalated blood and determining the clotting time of various mixtures of normal and hemophilic plasma after recalcifying. It was found that instead of the normal plasma causing clotting of the hemophilic plasma, the hemophilic plasma had acquired the property of markedly retarding the clotting of normal plasma. This was found to be the case at various times during the period over which transfusions were given. The clotting times of various mixtures at different times during this period are shown in Table 2. These data show that at this period the hemophilic blood contained a constituent which was inhibitory to the normal clotting process.

TABLE 2.—THE CLOTTING TIME OF MIXTURES OF NORMAL AND HEMOPHILIC PLASMA AFTER RECALCIFICATION WITH 0.1 CC. OF 0.5% CALCIUM CHLORIDE

Hemophilic plasma (cc.)	Normal plasma (cc.)	Clotting time at dates shown									
		10-10-41		10-11-41		10-14-41		11-3-41		1-8-42	
		Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
0.5	0.0	2+	..	2+	..	3+	..	1+	..	2+	
0.4	0.1	2+	..	..	55	..	50	..	45		
0.3	0.2	2+	..	..	50	..	45	..	45		
0.2	0.3	1	50	..	50	..	30	..	45		
0.1	0.4	..	45	..	17	..	14	..	20	..	45
0.0	0.5	..	3	..	4	..	3	..	3	..	3

This constituent may be the antithromboplastin reported by Tocantins[7] to be the cause of the prolonged clotting time in hemophilia. It is possible that transfusion of normal blood, by supplying an increased amount of thromboplastin to the hemophiliac, reduces the amount of circulating antithromboplastin and thereby causes a temporary improvement. Subsequently, however, the antithromboplastin returns not only to its previous level but to one higher than existed before the transfusion. As a result of this a second transfusion has less effect than the first. With time, the abnormally elevated antithromboplastin returns to its initial level and at this point a transfusion again becomes effective.

Summary. The failure of repeated transfusions of blood and plasma to produce any improvement in the condition of a hemophiliac is described and a possible explanation offered.

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THE TREATMENT OF AGRANULOCYTOSIS WITH SULFADIAZINE

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SINCE the introduction of prontosil and each of the subsequent "sulfa" drugs, much emphasis has been placed upon their possible toxic effects on bone marrow with development of agranulocytosis in susceptible individuals. Many authors have emphasized the necessity of discontinuing the drug immediately when blood counts in a patient receiving any sulfonamide show evidence of leukopenia. Some have observed only a transient leukopenia in patients receiving sulfonamides

with the white counts returning to normal levels despite the fact that the drug was continued.

The occurrence of agranulocytosis following the administration of drugs, especially amidopyrine and the benzamine group, has been known for some years. Since the introduction of prontosil many cases are on record in which each one of the sulfonamide group of drugs has been the etiologic factor in the development of this condition. Sulfanilamide and sulfapyridine have been the most frequent offenders, while relatively few instances have been reported in which agranulocytosis has been due to sulfathiazole[2,11,12] or sulfadiazine.[3,6]

Some patients with agranulocytosis recover spontaneously. In the fatal cases death probably is due to an overwhelming infection resulting from the absence of neutrophils and the loss of the body's normal defensive mechanism, the oropharyngeal ulceration and sepsis being only terminal phenomena.

The treatment of agranulocytosis, whether due to a drug, toxin or infection, has been unsatisfactory. Transfusions, liver extract, pentose nucleotides, etc., have had little effect in changing the usually fatal outcome of the disease. When agranulocytosis has occurred in the course of an infection treated with one of the sulfonamides the first thought, based upon the cumulative warnings published since the introduction of prontosil, is to discontinue the sulfonamide and to hope for spontaneous recovery following the usual treatment. However, it has been noted that the depression of white counts in some patients receiving sulfonamides may be only temporary, with an early return to normal levels even though the drug is continued. Further, the sulfonamides, especially sulfathiazole and sulfadiazine, have been used with beneficial results in the treatment of miscellaneous infectious processes with an associated leukopenia, and in some patients with agranulocytosis.[4,8,10] The bacteriostatic effect of these drugs apparently is independent of the granulocytes and may be just as effective in a patient with leukopenia or agranulocytosis as in one with a marked leukocytosis. Thus, in an individual without demonstrable granulocytes and with an overwhelming sepsis likely to cause death, the use of sulfonamides to combat the bacteremia seems logical if the maturation arrest due to previous sulfonamide administration is only a short-lived phenomenon. Successful treatment or prevention of the sepsis may tide the patient over the period of temporary bone marrow depression until the return of his normal granulocyte defenses.

We are presenting 3 cases of agranulocytosis in which we believe the successful outcome in each instance was due to the administration of large amounts of sulfadiazine.

Case Reports. CASE 1. A. L. H., a 26 year old, single, aviation cadet, was admitted to the hospital on October 24, 1942, complaining of chills, fever, and malaise of approximately 48 hours duration. The past history was negative except for the occurrence of measles, mumps and pertussis in childhood. On entry, examination showed the following: height, 65½ inches; weight, 145 pounds; temperature, 102.8° F.; pulse, 96 and respirations, 22. There was moderate redness of the pharynx with some associated cervical lymphadenopathy. The chest was clear. There was no rash. The remainder of the

physical examination was normal. The urine was negative. The white blood cell count was 13,300 with 75% segmented polymorphonuclear leukocytes, 5% juvenile forms, 17% lymphocytes, 2% monocytes and 1% basophils. Culture of the throat produced a hemolytic streptococcus, Lancefield type A, sub-group 12 (Griffith). The admitting diagnosis was nasopharyngitis though the possibility of early scarlet fever was considered likely. A mild scarlet fever epidemic was prevalent at the time. Forty-eight hours after admission the patient developed a strawberry tongue and a fine, punctate, erythematous rash typical of scarlet fever. On the fourth hospital day fine râles, with associated decreased intensity of the breath sounds, were heard over the right middle lobe. There was gradual fall of the temperature to normal by the 6th day and his chest was clear. Sulfadiazine had been started on admission, 1 gm. 6 times daily for 2 days then 4 times daily thereafter. From the 7th until the 11th hospital day the patient felt fairly well, remained afebrile, and the rash faded. The leukocyte count dropped to 6400 (43% polymorphonuclear leukocytes) on the second afebrile (8th hospital) day.

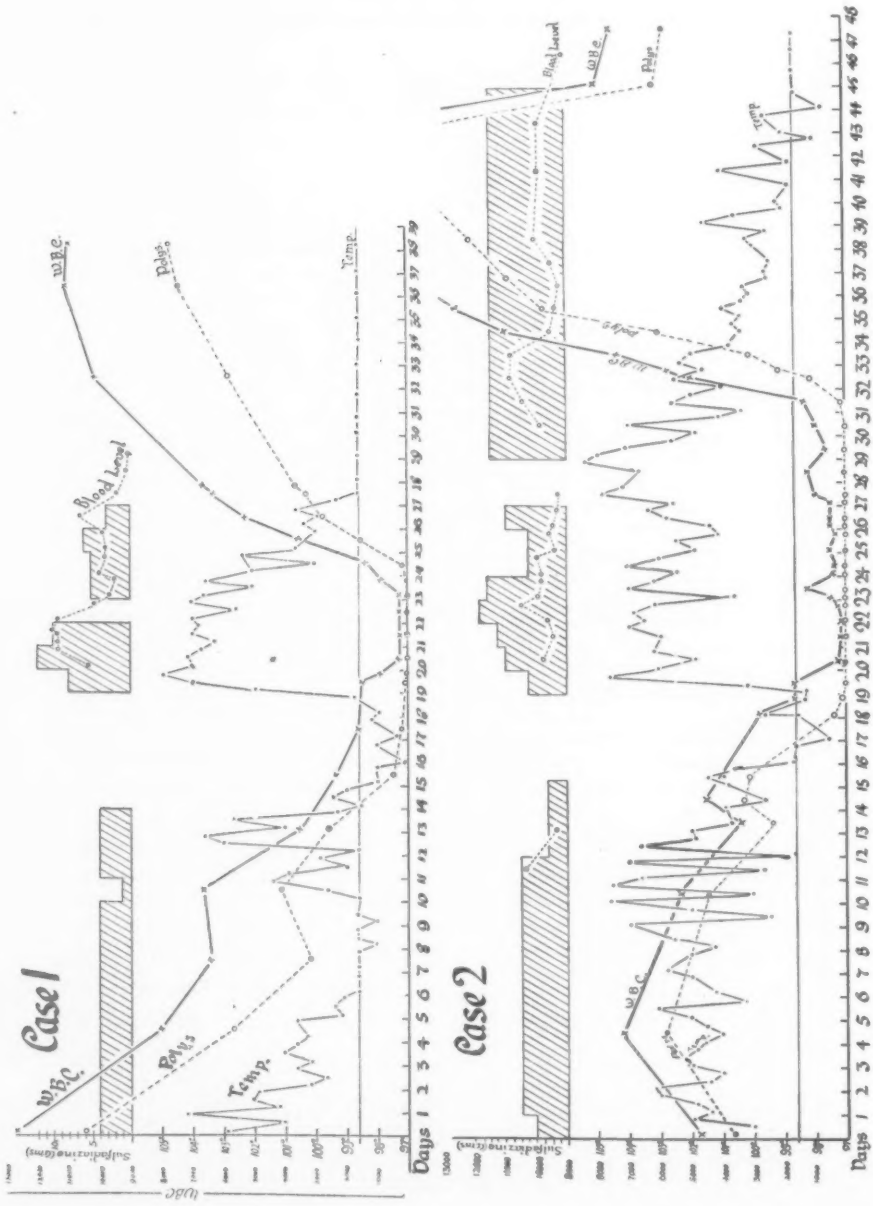
On November 3rd (11th hospital day) there was a recurrence of fever (101.2° F.) with associated reappearance of the scarlatiniform rash together with the return of a few râles over his right middle lobe. We considered this episode as a recrudescence of scarlet fever, rather than a reinfection, since the same type and strain of streptococcus was cultured from every other scarlet fever patient on the ward at that time. The W.B.C. count on the day of this recurrence had risen to 6800 (67% polymorphonuclear leukocytes).

During the next 4 days there was an irregular temperature elevation to 103.2° F. and a return of sore throat. The temperature was normal on November 7 (15th hospital day) and the patient again felt fairly well. The W.B.C. count, however, had dropped to 3550 (72% polymorphonuclear leukocytes) on November 6. Sulfadiazine was discontinued after a total of 58 gm. had been given. On the 16th hospital day there was a further drop in the count to 2300 (23% polymorphonuclear leukocytes). Twenty-four hours later the count had reached 1600 (13% polymorphonuclear leukocytes). By this time the rash had faded, desquamation had occurred, and the lung was clear of râles. The administration of liver extract, 2 cc., and pentnucleotide, 10 cc., intramuscularly twice daily was started. The daily administration of 200 mg. of cevitamic acid intravenously was begun. These measures were with no apparent effect since there was a continued fall in the count of all of the white blood cell elements.

By November 11 (18th hospital day) the W.B.C. count totaled 2250 and no polymorphonuclear leukocytes could be found in the many smears examined. There was a sudden rise in temperature with reappearance of sore throat and cough productive of mucopurulent sputum. On that day 250 cc. of citrated whole blood was given. On the next day, November 12, the patient's condition was worse, his temperature ranged from 103° to 105° F. and it was apparent that he probably would not survive. Believing that death from overwhelming infection would probably occur and surmising that possibly the agranulocytosis might be consequent to the effects of the hemolytic streptococcus and not to the drug, it was reasoned that if infection could be held in abeyance long enough, the bone marrow would recover and the patient might be given a chance for survival. Accordingly, the use of liver extract, pentnucleotide, cevitamic acid and transfusions, was abandoned. Sodium sulfadiazine was given intravenously twice daily in amounts sufficient to raise the blood level to 20 to 25 mg. per 100 cc. At the same time the use of convalescent scarlet fever human serum was begun. This was given in doses of 100 cc. daily for the next 11 days.

During the first 3 days (19th, 20th and 21st hospital days) of treatment with sodium sulfadiazine and serum the patient remained in a critical condition, his temperature was held at 103° F. or higher, and he developed ulcerations of the mucous membranes in the faucial regions and at the anus. By November 15 (22d hospital day), after 3 days of such treatment, icterus appeared, the R.B.C. count dropped from 5.1 million to 3.75 million with the hemoglobin

falling from 16.4 to 11.8 gm. per 100 cc. In an effort to halt the progrses of hemolysis sulfadiazine was discontinued for 1 day (November 15) to allow the sulfadiazine to fall to a lower blood concentration. Resumption of the drug on November 16 maintained the blood level between 5 and 10 mg. per 100 cc. From November 12 to 15 the total W.B.C. count varied from 200 to 310, all lymphocytes. No polymorphonuclear leukocytes could be seen in any of the smears examined. The first suggestion of recovery of the bone marrow did not



occur until November 17, after 5 days of complete absence of granulocytes, when the total count rose to 1470, and of 100 cells counted 98 were lymphocytes and 2 immature granulocytes. Thereafter, there was a rapid rise in all of the W.B.C. elements so that by November 21 (28th hospital day), there was no evidence of any blood dyscrasia.

Coincidental with the signs of improvement in the blood picture, the temperature began to fall gradually, reaching normal on November 20, 9 days after the onset of the third febrile episode. Physical signs and Roentgen ray evidence of pneumonia involving the posterior aspect of the right lower lobe first appeared on November 17. These signs cleared rapidly with the fall of the fever. Although sputum was by then rusty, no pneumococcus could be typed. A hemolytic staphylococcus was recovered from the sputum and the throat lesions.

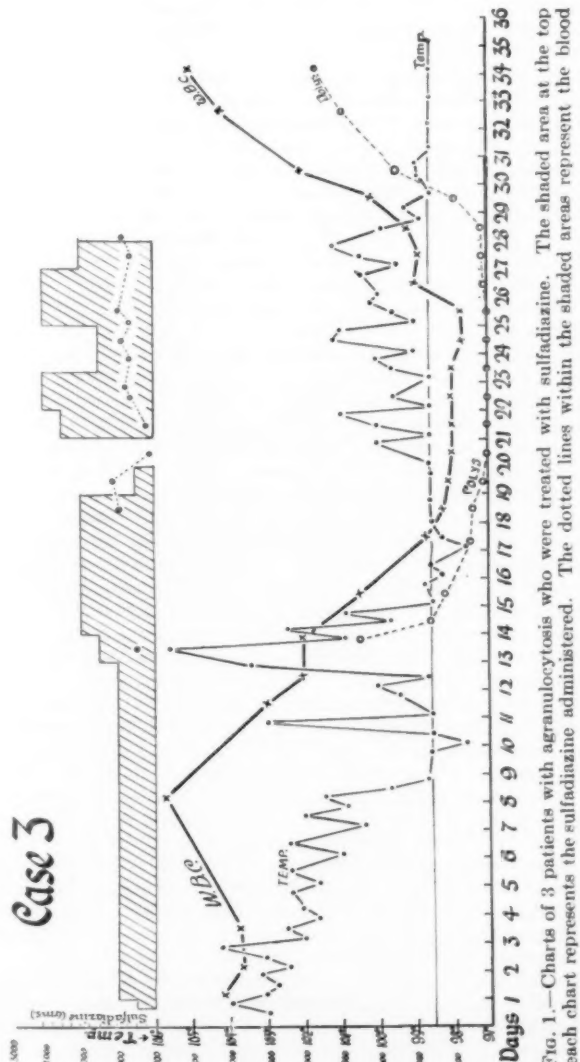


FIG. 1.—Charts of 3 patients with agranulocytosis who were treated with sulfadiazine. The shaded area at the top of each chart represents the sulfadiazine administered. The dotted lines within the shaded areas represent the blood sulfadiazine levels.

Except for a right inguinal adenitis which occurred as a complication of the anal ulceration, the hospital course subsequent to the return of the blood picture was uneventful. The patient, fully recovered, was discharged from the hospital on December 22, approximately 2 months following admission. Six weeks later (February 3, 1943) this patient again was hospitalized with an acute follicular tonsillitis of 2 days duration. A strain of hemolytic streptococcus was cultured from his throat. He had a normal response to sulfadiazine and was afebrile after 5 days. During this time 35 gm. of the drug were given. The patient ran the normal expected leukocytosis during the first few days of the infection and there was no demonstrable effect on the blood picture. He was discharged on February 14, fully recovered.

Case 2. K. H. K., a 24 year old aviation cadet, was admitted to the hospital on November 14, 1942 complaining of sore throat, dry cough, headache, and malaise of 2 days duration. The past history was not relevant. On admission the examination showed the following: height 71¾ inches; weight 185 pounds; temperature 101.4° F.; pulse 108; respirations 24 and blood pressure 110/70. There was moderate pharyngitis. The lung fields were clear. The remainder of the examination was normal. The urine was negative. The white blood cell count was 4700 with 70% segmented forms, 6% juvenile forms, 21% lymphocytes and 3% monocytes. The admitting diagnosis was nasopharyngitis. During the first 16 days of hospitalization the patient was only modertaely ill, his temperature ranging from 100° to 104° F. On the 3d hospital day signs of pneumonia involving the right lower lobe were evident. Because of the clinical course, the absence of any specific bacterial flora in the sputum, and the absence of leukocytosis, it was considered that the pneumonia was of the "virus" type. During this episode the patient received a total of 76 gm. of sulfadiazine. Other medications administered were potassium iodide, codein and aspirin.

From December 1 to 3 (17th to 19th hospital days) the patient was afebrile and felt improved. The Roentgen ray showed considerable clearing of the pneumonia. Whereas the white blood cell counts had ranged from 3550 to 5700, with a normal differential picture during this first febrile illness, there was a sudden drop to 2650 with 12% polymorphonuclear leukocytes on December 3. By the next day the count had dropped still further to 1300 with only 1% polymorphonuclear leukocytes. At the same time the temperature abruptly rose to 104.6° F. and there were physical signs and Roentgen ray findings of pneumonia, this time in the right upper lobe. Soon thereafter the typical necrotic throat lesions, characteristic of agranulocytosis, appeared. From December 4 through December 12 (20th to 28th hospital days) the W.B.C. count ranged from 130 to 1050 cells per c.mm., all lymphocytes. Not a single polymorphonuclear leukocyte could be found during this time. On December 13, a few juvenile forms were observed and thereafter there was a rapid return of the blood picture to normal.

Because of our experience with Case 1 it was felt that resumption of the use of sulfadiazine might save this patient from overwhelming bacterial infection. Beginning December 4 (20th hospital day) the drug was given in a dosage sufficient to maintain the average blood concentration between 5 and 10 mg. per 100 cc. By December 11 (27th hospital day), after 8 days of such treatment, 64 gm. of the drug had been given. A new area of consolidation had appeared at the left base and the patient was still critically ill, having run an extremely stormy course with high fever. At that stage there was no evidence of return of the blood to normal, and the authors, being rather faint at heart, stopped the drug again. By December 13 (29th hospital day) the patient had been 2 days without sulfadiazine. Even though a few polymorphonuclear leukocytes were reported for the first time, the patient was worse. There was further spread of the pneumonia to the previously cleared right lower lobe, the temperature rose to 105.6° F., auricular fibrillation appeared and with it additional respiratory embarrassment due to congestive cardiac failure. The patient was comatose and deeply cyanotic and it seemed that he could survive for only a few more hours. Rapid digitalization and the use of oxygen con-

tributed some relief to the cardio-respiratory difficulties. Since discontinuance of sulfadiazine was considered a factor in the increased severity of the illness, its use was resumed for the third time in a dose of 10 gm. daily. With reinstitution of this treatment there was evidence of beginning recovery of the bone marrow as shown by the appearance of juvenile polymorphonuclear leukocytes in increasing numbers in the blood. By December 20 (36th hospital day and the 6th day of the third course of sulfadiazine), the count had risen to 14,150 with 85% polymorphonuclear leukocytes. With the progressive rise of the count there was an associated fall in the fever and general improvement. By December 29 (45th hospital day) the patient was afebrile and sulfadiazine was discontinued. One hundred and fifty gm. of the drug had been given over a 15-day period during this third course of treatment; 290 gm. had been given throughout the entire hospital stay.

Because of the development of a moderately severe hemolytic anemia with fall of the hemoglobin level to 9 gm. per 100 cc. two whole blood transfusions of 500 cc. each were given on December 12 and 14. Donors who had recently recovered from "virus" pneumonia were used. In addition a total of 1800 cc. of human convalescent "virus" pneumonia serum was given in divided doses intravenously every 3d day from December 6 through December 20 (22d through 36th hospital days). Liver extract was given in 2 cc. doses intramuscularly daily from December 4 through December 10. Recovery, after return of the blood picture to normal, was uneventful. After 1 month his strength had returned, he had nearly regained his weight and there was no evidence of any blood dyscrasia.

Case 3. A. J. B., a 22 year old aviation cadet of Mexican descent, was admitted to the hospital on December 9, 1942 complaining of headache, chilliness and dry cough of 4 hours duration. The past history was not relevant.

On admission the physical examination revealed the following: height, 68½ inches; weight, 160 pounds; temperature, 103° F.; pulse, 100; respirations, 22. There was a dry nasopharyngitis and paroxysms of cough were frequent. The lung fields were clear to auscultation. The remainder of the examination was normal. The urine was negative. The W.B.C. count was 7150 with 77% polymorphonuclear leukocytes, 22% lymphocytes, and 1% monocytes. The hemoglobin was 15.2 gm. per 100 cc. The Roentgen ray showed pneumonic infiltration in the lower left perihilar region and in the right lower lung field and "virus" pneumonia was diagnosed.

The patient was moderately ill with daily peaks of temperature to 102.6° to 104° F. for the first 8 hospital days. On December 18 to 19 (9th and 10th hospital days) there was no fever and the patient felt much better. However, on December 20 (11th hospital day) there was return of fever with the associated signs of spread of pneumonia to the lower portion of the left lung. This second febrile episode was more severe than the first, being accompanied by more prostration, severe cough, and cyanosis requiring the use of oxygen. The dosage of sulfadiazine, which had been administered since admission (4 gm. daily) was doubled. On December 24 (15th hospital day) the temperature abruptly returned to normal after a febrile period of 4 days.

Whereas the blood picture had been previously normal a drop of the W.B.C. count to 2500 with 56% polymorphonuclear leukocytes was first noted on December 23. By December 26 (17th hospital day) it had dropped to 1800 with only 22% polymorphonuclear cells. Sulfadiazine was discontinued on the next day, December 27, after a total of 86 gm. had been given. Thenceforth the W.B.C. counts ranged between 600 and 1750 (all lymphocytes with absolutely no polymorphonuclear leukocytes) until January 6, 10 days later, when the first sign of bone marrow recovery was evident in the abrupt rise in the W.B.C. to 2850 with 3% immature polymorphs. Thereafter the blood picture rapidly returned to normal. The count on January 11 (33d hospital day) was 7400 with 48% adult polymorphs, 4% young polymorphs, 46% lymphocytes, and 2% monocytes.

During the period of complete absence of polymorphonuclear leukocytes there was a daily temperature elevation to 100° to 101° F. This disappeared

on the return of the blood to normal. In spite of the blood changes the pneumonia progressively cleared at this time. No throat lesions developed although there was clinical evidence of a moderately severe catarrhal laryngitis. With the return of the W.B.C. count to normal, sulfadiazine was discontinued (January 5, the 27th hospital day) after 60 gm. had been given over a 7 day period and after a total of 146 gm. had been given during the entire hospital stay.

Recovery, after the return of the blood to normal, was uneventful.

Comment. In each of the 3 patients there are common factors. Sulfadiazine in total dosages varying from 52 to 72 gm., had been given over a fairly protracted period early in the course of each man's illness. At the time blood counts disclosed granulocytopenia each patient still revealed clinical evidence of infection. The lowering of the total white count with the complete absence of granulocytes in the peripheral blood, forewarned the stormy course that was to follow. In the first 2 patients especially, the infections extended to nearly overwhelming proportions. It seemed obvious that these young men would die unless the original infectious process and the later uncontrolled spread of infection were held in check during the period required for the temporary bone marrow depression to subside.

Since Case 1 failed to respond to the usually recommended treatment for agranulocytosis it was suggested that perhaps we were erroneous in assuming that the blood changes were due to the drug but that instead, the streptococcus toxin might be the etiologic agent. If this were correct, the drug might well be resumed, offering some hope of controlling the infection pending recovery of the bone marrow depression. Our knowledge at that time of only one case report[3] of agranulocytosis due to sulfadiazine added weight to this opinion and further influenced our decision to administer large amounts of sulfadiazine. We were further stimulated in carrying out our plan of treatment when we learned from Dr. Madeline Fallon of Los Angeles that she had used sulfonamides with apparent success in several children with agranulocytosis which, in her opinion, had been induced by infection. The patient's dramatic recovery was gratifying.

Our assumption that the strain of hemolytic streptococcus causing the scarlet fever in Case 1 also produced the agranulocytosis appeared erroneous when Cases 2 and 3 developed agranulocytosis during the course of pneumonic infections of virus etiology. The occurrence of agranulocytosis as the result of virus pneumonia or other virus infections has not been reported to our knowledge. On the other hand, sulfadiazine occasionally has caused agranulocytosis and each of our 3 cases received moderate doses of sulfadiazine for 2 or more weeks prior to the onset of bone marrow depression. We now are convinced that the drug was the responsible agent in producing agranulocytosis in each of our cases.

The remarkable response in these cases demonstrates that despite the primary rôle played by sulfadiazine in causing agranulocytosis, the bone marrow can recover from the temporary depression even with continued or subsequent administration of large amounts of the same drug. This approach to the treatment of agranulocytosis is unique in

view of the constant warnings in the literature to discontinue sulfonamides immediately upon the first evidence of an impending granulocytopenia. Based upon our experience with this small but striking group of cases we believe that the patient who develops agranulocytosis, regardless of the etiology, should not be deprived of the most effective means of combating complicating sepsis but should be given one of the sulfonamides, preferably sulfadiazine, in amounts sufficient to maintain a blood level of approximately 10 to 20 mg. per 100 cc., until such time as the temporary bone marrow depression is overcome and the normal protective mechanisms are again functioning. Sulfadiazine is recommended because, of all the sulfonamides, it is least apt to cause serious toxic reactions.[1,5,6,7,9,13]

Summary. Three cases of severe agranulocytosis due to sulfadiazine were treated successfully with large doses of sulfadiazine. The agranulocytosis occurred during the course of acute infections (scarlet fever in 1 case and primary atypical virus pneumonia in 2 cases). Each patient had received moderate doses of sulfadiazine for 2 or more weeks prior to the onset of bone marrow depression. Transfusions, pentose nucleotides and liver extract in Case 1 were without any demonstrable beneficial effect. Convalescent human serum was used as an adjunct to the sulfadiazine therapy in each of the 3 patients while oxygen was administered in Cases 2 and 3. Even though the infectious processes may have played a part, sulfadiazine probably was the primary factor in causing the agranulocytosis. However, the subsequent administration of large amounts of the same drug seemed responsible for the ultimate recoveries.

Conclusions. 1. Cases of agranulocytosis due to sulfadiazine administration during acute infections may be aided by subsequent dosage with the same drug.*

2. Spontaneous regeneration of polymorphonuclear leukocytes by the depressed bone marrow can occur during the administration of large amounts of sulfadiazine even though this drug was responsible initially for the depression.

3. Sulfadiazine is effective in controlling sepsis which usually accompanies agranulocytosis.

* Another patient, M. J. B., developed granulocytopenia, but not complete agranulocytosis (lowest W.B.C. count was 1750 with 2% polymorphonuclear leukocytes, 1% eosinophils and 97% lymphocytes) 1 week after having received sulfadiazine (52 gm. in 12 days) for moderately severe scarlet fever. Ten days after admission to the hospital this patient developed the enanthem, followed in 48 hours by the exanthem characteristic of measles. The leukopenia which occurred at the time of his measles infection did not seem significant. However, subsequent W.B.C. counts revealed a gradual lowering of both the total W.B.C. count and the granulocytes until the lowest level was attained on the 28th hospital day, 10 days after the disappearance of his measles rash and 15 days after discontinuing the sulfadiazine. A mild throat infection was the only complication. Sternal puncture revealed many immature granulocytes. Because of the absence of significant fever (highest temperature 100.2° F.) and other evidence of sepsis, and because this patient did not develop complete agranulocytosis, we did not believe sulfadiazine was necessary. His complete recovery with a normal W.B.C. count and differential (7000 W.B.C. with 53% polymorphonuclear leukocytes, 43% lymphocytes, 2% eosinophils and 2% basophils) 10 days later, emphasizes the fact that some patients with a temporary depression of the bone marrow will recover spontaneously. Only when severe infection is imminent is sulfadiazine therapy necessary.

4. In spite of previous warnings to the contrary, the use of sulfadiazine may be advisable in the treatment of agranulocytosis, irrespective of the cause, if infection is either present or imminent.

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ACUTE TRAUMATIC HEART DISEASE

A Case of Myocardial Contusion With Recovery

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The following case of acute traumatic heart disease seems worthy of reporting because of its rarity and because in this instance there is little likelihood of preëxisting heart disease. This patient was observed early, and an essentially normal electrocardiogram was obtained at the onset. A series of tracings was obtained which revealed serial changes that are pathognomonic of myocardial injury. This may have been merely a cardiac muscle contusion, or, as seems less likely to us, this contusion progressed to a myocardial infarction. There is little reason to believe that any degree of coronary artery occlusion occurred.

Case History. V. B. T., a white aviation cadet of 22 years, was admitted to the Station Hospital, SAAAB (Reg. No. 3831 and 4004), August 15, 1942, complaining of pain over the lower portion of the sternum, dyspnea, and of constricting chest pain with radiation to the jaw. These symptoms had been present and increasing in severity for 11 hours. Twenty-four hours before entry he had received a blow over the lower sternum from the elbow of a fellow student while playing football. This blow, as he described it, was strong enough to stun him and throw him to the ground, but in a few seconds he resumed play and his symptoms appeared approximately 12 hours later. Examination disclosed tenderness and edema over the lower portion of the sternum, but no evidence of fracture was obtained by Roentgen ray examination.

The family history was irrevelant; the past history gave no indications of congenital or of acquired heart disease. There had been no serious infections and there were no suggestions of the rheumatic syndrome. The usual aviation cadet health survey and physical examination had been made a few days prior to the accident and no gross abnormalities were found. The examination included Roentgen rays of the heart as well as strenuous functional tests.

Upon admission the patient was somewhat dyspneic and was more comfortable in the sitting position. The oral temperature was 99.6° F., pulse 110, respirations 20; the skin moist and warm. Forceful pulsations were noted in the blood-vessels of the neck. Blood pressure 140/75. He complained of pain radiating to the left side of the neck and jaw, and also to the tip of the left shoulder. This pain was made worse by deep inspiration and by movements of the trunk. The lower portion of the sternum, with its overlying edema, was exquisitely tender. In the left axilla there was decreased resonance and the breath sounds were partially suppressed. The area of cardiac dullness was considered to be somewhat increased and the heart sounds faint. The rhythm was regular. There was moderate epigastric rigidity, but no abnormal tenderness.

The initial Roentgen ray examinations seemed to be within normal limits. However, comparison at a later date with studies of his chest made at his initial examination for cadet training showed the cardiac outline to be larger than before. One day later a small amount of fluid at the left costophrenic angle was revealed by Roentgen ray; but this had decreased in amount by the third hospital day. The first electrocardiogram was normal, save for a suggestion of elevation of the RS–T segment in Lead II.

The fever reached a peak of 100.4° F. on the second hospital day, but he was afebrile after the third day. The local and general symptoms rapidly disappeared and the pleural fluid decreased. The blood pressure before discharge was 115/65. At this time it was considered that there might be a small amount of blood within the pericardium, but as the patient was free of symptoms and seemed quite well he was discharged August 21.

Two days later the patient was readmitted to the hospital in a semistuporous condition with dyspnea, cyanosis and orthopnea. A few hours before he had suddenly developed severe precordial pain which again radiated into the neck and also into the interscapular region. His initial dyspnea had been rapid in onset and most severe.

When examined there was evident respiratory distress, and numerous crepitant râles were present at both lung bases. The heart seemed normal in size, was rapid, hyperactive, and regular. Blood pressure 120/80. During the first few hours a loud, rough, to-and-fro murmur was heard over the base of the heart, the diastolic elements being louder, and best heard at the third intercostal space just to the right of the sternum. There was also a short, soft systolic murmur at the apex. These murmurs, apparently associated with acute cardiac decompensation, were intermittently audible over a period of about 12 hours. Under morphine the pain was controlled, and the pulse, which was always regular, dropped from 130 to 112; the respirations fell to 24 and the temperature to 99.4° F.

On the day following the second admission the heart was found to be further enlarged by Roentgen ray when compared with the previous examinations, and there was evident vascular congestion at both lung bases. Some fluid had reappeared at the left base.

No significant abnormalities were found upon laboratory examination of the blood or urine. Repeated determinations of the erythrocyte sedimentation rate were well within normal limits. Two blood cultures were sterile.

The remainder of the patient's course in the hospital was stormy and protracted, in that excitement and exertion brought on dyspnea, tachycardia, and early signs of decompensation. Recovery from each attack, however, was rapid. A 60 day furlough was granted on October 19, 1942, and during this period the patient was free of dyspnea and pain. He remained entirely comfortable, his strength returned and he was even able to attend dances. There

was a moderate increase in body weight. Occasionally momentary twinges of pain were felt in a spot 8 cm. below the left nipple, these always being associated with twisting the trunk or with stretching the left side of the body. This pain has never been related to exertion or emotion.

At examination December 19, 1942, the patient gave the appearance of normal health. Blood pressure 120/80. No cardiac abnormalities were made out upon auscultation. Roentgen ray examination revealed the heart size and shape to be just as it was before injury and the lungs were clear. Upon fluoroscopic examination the cardiac pulsations were of good quality and amplitude along the left border; there was a suggestion of slightly weaker pulsations at the right border. There were no pericardial or diaphragmatic adhesions.

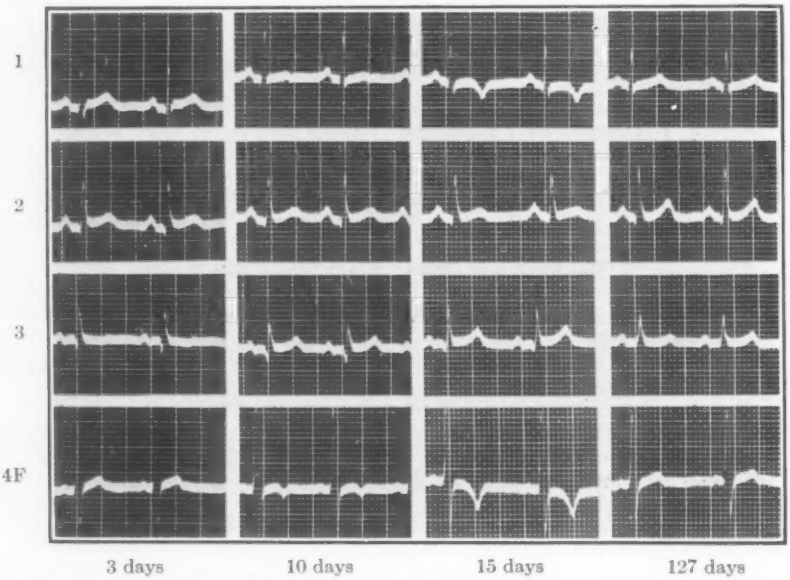

FIG. 1.—Serial electrocardiograms following a blow over the precordium of a healthy young man. Deep late inversion of T in Leads 1 and 4F is seen to reach a maximum at 15 days, with later return to normal configuration.

Reëxaminations of blood and urine were normal. The erythrocyte sedimentation rate was 2 mm. in 1 hour. The basal metabolic rate was +6%.

The EKG was normal, T4F now being upright, with further increases in the amplitude of the upright T2 and T3.

Discussion. Medical literature regarding acute traumatic heart disease is still confused. This is due, in part, to rapid change in terminology which has lead to inaccuracy in the use of terms. Thus, it is obvious that until very recently "coronary artery occlusion" and "myocardial infarction" have been used synonymously. Only in recent articles has there been indication that authors considered the possibility that coronary artery occlusion could occur without myocardial infarction; or conversely, that myocardial infarction could occur without acute coronary artery obstruction. A further difficulty is that most of the writing has been chiefly the reporting of case histories,

and these have been borrowed back and forth in a repetitious manner to such an extent that in reading papers one comes across the same history 5 or 6 times. Many of the case histories are inadequate and the associated comment frequently is irrelevant.

The standard textbooks on heart disease have little information regarding non-penetrating injuries of the chest producing heart damage. Stroud's recent textbook, however, has an excellent chapter by Hugh Barber.[1] White and Glendy[26] have contributed a chapter in Brahdy and Kahn's "Trauma and Disease" which contains an excellent general discussion and an adequate review of the literature. It is especially valuable for its critical review of the experimental literature upon traumatic cardiac disease. Warburg's monograph[24] published in 1938 is disappointing in that he has been more interested in the historical aspect of the problem and has merely compiled those instances of cardiac trauma already recorded in the world's literature. He does point out cases of traumatic heart damage which were reported in the latter part of the 17th century. Up to the beginning of the 20th century, 64 cases were on record. He finds 197 cases in the first 37 years of the 20th century. Fischer,[6a] in 1868, reported 452 cases of traumatic cardiac lesions, of which 76 were due to non-penetrating injury. Seven were considered to be cardiac contusions and 64 were cardiac ruptures. There was only 1 autopsy.

It is evident that even yet we have no satisfactory evidence regarding the incidence of cardiac contusion. It is usually thought to be very rare and the majority of the recorded cases have ended fatally. Experimental evidence indicates that most of the injuries should result in recovery. From this apparent discrepancy it is difficult to avoid the conclusion that the majority of the instances of cardiac contusion are not recognized. Thus, Stroud[22] is quoted as saying: "This subject is most important from the standpoint of insurance compensation; I still feel cardiac disease is unusual following anterior chest trauma." However, the same author, in editing a textbook on heart disease has included a long and well-written chapter on the subject. The point of view of its author is that cardiac contusion is of frequent occurrence. White[26] states that among 7600 autopsies at the Massachusetts General Hospital, which includes a busy accident service, there is not a single case of cardiac trauma on record as of March, 1936. Sanders[20] says that the combined records of the hospitals in Memphis contain no record of cardiac contusion, in a total of 326,500 admissions. Among these same admissions there were 10 penetrating wounds of the heart.

Excellent articles on the subject of cardiac contusion have been contributed by Beck,[2] Sigler,[21] Tuohy and Boman,[23] Kahn and Kahn,[8] and Leinoff.[9,10,11] The work of Bright and Beck[4] contains not only an adequate review, but their own experimental evidence.

Summary. 1. An instance of myocardial contusion with recovery is reported.

2. The symptoms, clinical course, and electrical deviations are similar to those of acute myocardial infarction.

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A SOLITARY CALCIFIED CYST OF THE SPLEEN

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Two clinical entities should be thought of when the radiologist encounters a large annular calcification in the left upper abdomen. The first is a solitary calcified cyst of the spleen; the second, an aneurysm of the splenic artery. Solitary cysts of the spleen are not exceedingly rare;[11] calcified cysts are rare; aneurysm of the splenic artery is more common than one would think—at least 90 cases have been reported.[1,5,6]

Case Report. Miss B. M., white, female, aged 60, came to my office on December 29, 1941, complaining of itching eyelids. She had lost 28 pounds in the past 4 years and had a decided subicteric tinge. The pruritus was undoubtedly due to the jaundice. She had a second complaint of severe paroxysmal headache, usually localized to the left frontal region, rather typical of migraine, as it had been present over a long period of years.

Two years before, a lesion of the gall bladder had been reported after Roent-

gen ray examination. (The calcified ring in the splenic region is said to have been absent at that time.) Now in 1941 fullness was found in the left upper quadrant, with the definite suggestion of a mass on deep inspiration. Physical examination was otherwise negative. Her blood count on 12–30–41 was: hemoglobin, 61%; erythrocytes, 4,260,000; color index, 0.7+; leukocytes, 7400; neutrophils, 54% (segmented, 31% [young form, 1%]; non-segmented, 23%; lymphocytes, 39% [small]; 3% [large]; monocytes, 3%). Her icterus index was 10.

In view of her previous history, the Graham test was repeated. A large spherical mass with a calcified periphery was found lying in the left upper quadrant, suggesting a solitary cyst of the spleen (Fig. 1). The left kidney had been displaced downward. The right kidney was normal in size, shape and position. The liver was normal in size. There was no evidence of a renal, ureteral or vesical calculus. The lumbar spine and pelvis were normal. Two other possibilities were suggested; an old echinococcus cyst of the spleen; cyst of the left lobe of the liver.

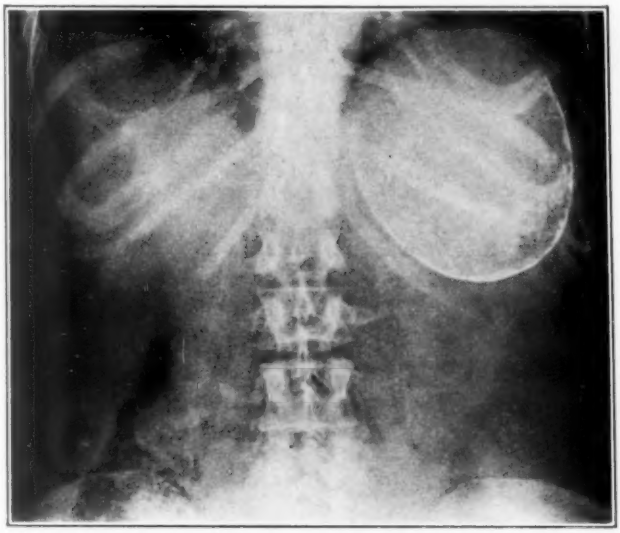

FIG. 1.—Large annular calcified shadow—left upper quadrant. Preliminary film of abdomen (1–2–42).

Roentgen ray examination of the gall bladder by means of the Graham test showed that the gall bladder took the dye moderately well. The shadow was homogeneous and there seemed to be an anatomic defect across the fundus—Phrygian cap. Following the fatty meal the gall bladder contracted about one-third.

Diagnosis. Solitary calcified cyst of the spleen. Normally functioning gall bladder—Phrygian cap.

To rule out the possibility of an echinococcus cyst an antigen was obtained and a scratch test made, which proved to be negative.

Laparotomy. On February 16, 1942, a hard calcified tumor the size of a grapefruit, occupying the spleen, was delivered with difficulty. The spleen and a small accessory spleen were removed.

Pathologic Report. The spleen was stretched thinly ($\frac{3}{4}$ inch in thickness) over part of the surface of a cyst which was almost spherical and measured 12 x 13 cm. in diameter. The surface of the spleen was smooth; of the cyst was shaggy. The cyst projected from the region of the hilum displacing the

vessels 2 cm. Its wall varied from 1 to 2 mm. in thickness, was rigid and calcified, with rough internal and external surfaces due to plaques of calcium.

FIG. 2.—Calcified cyst with the spleen lying over its distended surface. (Incisions are for histologic sections.)

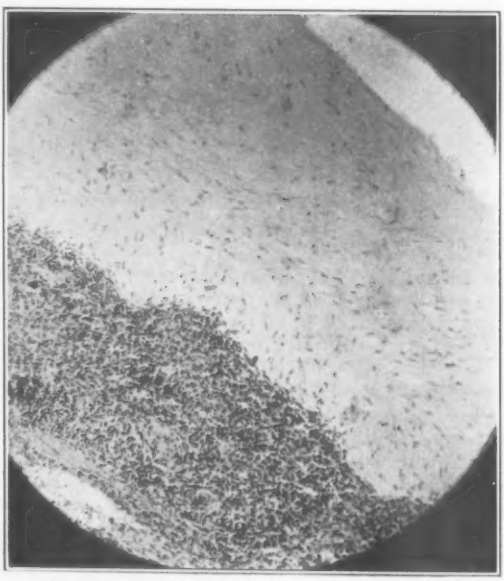

FIG. 3.—Histologic section of lining membrane.

The lining was smooth and contained 100 cc. of brownish turbid fluid with a glistening sheen suggesting cholesterol (Fig. 2).

Microscopic examination (Fig. 3) revealed a thick wall composed of collagenous fibrous tissue devoid of any epithelial lining. Plaques of calcified material were found. There was some lymphocytic infiltration in the laminated hyalinized fibrous tissue. The lymphoid tissue in the spleen itself was greatly decreased in amount. Numerous rather small vessels in one area suggest the possibility of hemangiomata, with rupture and hemorrhage as the possible cause of the pseudocyst.

Diagnosis. Solitary calcified cyst of the spleen.

COURSE. After 10 days of uneventful convalescence, the patient developed intense pain in the lower right chest with dyspnea and intense frontal headache. Her pulse became very rapid and weak. Her blood count on 3–3–42 revealed: hemoglobin, 55%; erythrocytes, 2,880,000; leukocytes, 4100; neutrophils, 70% (segmented, 67%; non-segmented, 3%); lymphocytes, 21%; monocytes, 7%; eosinophils, 2%. The prothrombin time was normal. Within the next 48 hours she developed a small area of thrombosis in the right superficial femoral vein and subsequently pain in the lower left chest. The chest condition was diagnosed as due to infarcts.

After splenectomy one expects the platelet count to rise, and embolism, thrombosis and infarction are the usual complications of this operation. We gave the patient heparin which prolonged her blood clotting time from 1½ minutes to 18 minutes. The blood platelets were 200,500 on 3–12–42, with a coagulation rate of 15 minutes. During her entire convalescence the leukocyte count never rose above 8250. The majority of the counts were around 4000. She made a slow recovery and is now perfectly well. No Howell-Jolly bodies were found, either before or after splenectomy.

Discussion. In the literature only 5 other cases of calcified cyst of the spleen could be found: Scotson,[9] Manchester, England (1933); Shawan[11] of Detroit (1937); Földes[4] of Germany (1927); Baumann and Kohnstamm[2] (1930); Culver, Becker and Koenig[3] (1942).

It is interesting to note the ages of the patients because one might expect calcification in the older age groups. Of these 6 patients the ages were 18, 25, 44, 49 (Földes[4]), 52 (Baumann and Kohnstamm[2]), 60 (my patient). Though other authors have stated that it was essentially a disease of females, 4 were females, 2 males.

The failure to find Howell-Jolly bodies after splenectomy is of interest in view of their occurrence, sometimes for many years (*cp.* O. H. P. Pepper's case[8a]); the finding is not constant in humans, however, and they are regularly absent in dogs after splenectomy.[8]

The position of the kidney on the affected side is interesting. In Shawan's[11] case the kidney was displaced upward. In my case it was displaced downward and was quite distinct and separate from the splenic shadow.

A very similar appearance is noted in calcified aneurysm of the splenic artery. The location is the same; the Roentgen ray appearance is the same. There is, however, one distinguishing clinical feature and that is a bruit. Pulsation may or may not be present in aneurysm.

There have appeared 2 reports of very similar cases in the *Journal of Radiology* while this paper was in preparation, 2 of which were aneurysms of the spleen,[10] and the third a calcified cyst of the spleen.[3]

From the surgical standpoint, operation on aneurysms of the splenic

artery is hazardous, with high mortality. It is not so hazardous on splenic cysts. It is important that the surgeon should know whether he is going to find an aneurysm of the splenic artery or a cyst of the spleen. Certainly the radiologist should advise the clinician of this possibility, and simple auscultation will readily make the differential diagnosis.

The purpose of writing this paper is to call the attention of the radiologist to the two possibilities which cannot be distinguished readily without listening for the bruit. Surgical intervention in aneurysm of the splenic artery is indicated. The mortality, however, is much higher than in solitary cyst of the spleen.

Roentgenologists will be interested in comparing the illustrations of this case with those presented in a case report by Montgomery[7] of a solitary cyst with a calcified wall in the *right* upper quadrant. We have little explanation for these cysts, but since they have been reported in children we must give considerable weight to the idea that they are fetal inclusions.

Summary. A calcified cyst of the spleen is reported, which it seems had probably developed since 1938. There is no record of its presence being observed in the films that were made at that time. Furthermore, the patient's itching and subicteric color were of recent origin, giving credence to the view that the cyst was of hemorrhagic origin and its calcification recent. We know that hematomas in muscle will calcify in 10 days so that there is no reason for us to postulate that this cyst was of congenital or juvenile origin.

Conclusion. The radiologist should be aware of two possibilities when annular calcified shadows are encountered in the left upper quadrant, namely, aneurysm of the splenic artery and calcified solitary cyst of the spleen. Second, the differential diagnosis can be made with the stethoscope. Third, aneurysm of the splenic artery and solitary cyst of the spleen are more common than the literature would indicate and should be given definite consideration in the presence of any left upper quadrant mass.

Grateful acknowledgment is made to Dr. Louise E. Keasbey, Pathologist, and Miss A. M. Falck for their assistance.

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INTRAVASCULAR PARATHYROID GRAFTS

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The striking clinical pictures presented by the endocrine deficiency diseases are well known to all. Yet the field of "replacement surgery," as it was termed by Harvey Stone in a recent review,[10] is still one of the most challenging problems of modern therapeutics.

During the years 1906–1908 Halsted[4] performed many transplants of thyroid and parathyroid tissues in dogs, achieving considerable success in the iso-grafting of the latter into the preperitoneal tissues of dogs. In the course of these experiments he also formulated the concept that is often referred to as "Halsted's Law"—*i. e.*, a physiologic need on the part of the host must be present if grafted tissue is to function. Recently some authorities have questioned the necessity of a preëxisting deficiency before grafting, Dunphy and Keeley[3] for example, having successfully iso-grafted adrenal tissue to the ovary of a dog whose other adrenal gland was still functioning. It has not been shown, however, that an animal with only one adrenal can be regarded as completely free of a deficiency.

On the basis of earlier work, Stone, Owings and Gey[11] in 1934 reported 2 cases of successful parathyroid cross-grafts in humans. From their experimental work on dogs, they had concluded that growing the tissue in the serum of the donor and the host as a preliminary to implantation was necessary before successful cross-grafts could be achieved. This method was also used by Houghton, Klassen and Curtis[5] in 1939 in a successful human parathyroid transplant. Over a period of 11 days, the graft was grown in a constantly changing media with an increasing proportion of the host's serum, and a decreasing proportion of the donor's serum. Both groups of workers used the axillary areolar tissue as the site of implantation.

In the past, other investigators had been attracted by more vascular organs such as spleen and kidney as logical beds for transplants. But because of this very vascularity and the postoperative formation of strangulating hematomata, they were forced to abandon these sites.

It appeared to us, however, that the fault lay primarily in the method of implantation rather than in the site selected, and that transportation of the grafts by the blood stream to the final bed might lessen the degree of postoperative hemorrhage. In 1933 Dinsmore,[2] in reviewing thyroid tumors and their intravascular metastases, gave excellent support for the efficacy of this method of grafting. Reid and Stevenson,[9] working at this clinic in 1936, attempted embolic grafting of

* Recently deceased.

parathyroid glands to the leg muscles of dogs via the femoral artery. There were no clear-cut takes in these animals.

Stone, in the review already referred to, states that "the bed should be of loose structure, otherwise tissue pressure will compress the graft." As a method was at hand which enabled us to invade the most vascular organs, the lungs seemed to answer admirably this second prerequisite, that is, looseness of structure. With the foregoing as a basis, the following experiments were performed.

Method. Mongrel dogs were used. Through a midline incision in the neck, both thyroid glands were exposed. The inferior pole vessels were divided at least 2 cm. from the gland. Using these vessels as pedicles, the glands were separated from the surrounding muscle by sharp dissection. The lateral and upper pole arteries and veins were also divided as far as possible from the gland. The four parathyroid glands were dissected free from the mass of tissue and cut into 2 mm. size fragments, in all cases 4 glandules having been found. These were injected into the external jugular veins which had been previously isolated through the same midline incision. In several of the earliest experiments the glands were placed whole in the opened lumen of the vein. In all cases the transplants were flushed down toward the heart with 200 cc. of saline.

TABLE 1.—RECORD OF 11 PARATHYROID ISOGRAFTED DOGS SHOWING FREQUENCY OF ADMINISTRATION OF CALCIUM AND PARATHORMONE FOR THE TREATMENT OF TETANY

Dog No.	Postoperative days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	Remarks
668	x x x x x x x x x x 0	
573	x x x x x x x x x 0	
617	x x x x x x	Sacrificed 6 months
566	x x x x x x x x x x x x x x 0	
634	x x x x x	Died 43 days
678	x 0	
620	x x x 0	
654	x 0	
633	x x 0	
621	Mild tetany on occasion—no therapy need	Sacrificed 5 months
644	x x x x x x x x x	Sacrificed 7 months
Total daily therapy	3 4 2 7 3 5 6 3 4 4 3 4 2 2 1 1 2 2 1 1 1 1 1 2	

Key: x, 10 cc. calcium gluconate and 1 cc. parathormone i.v. 0, dog died in tetany.

Results. Two groups of experiments were performed. Eleven dogs received their own parathyroid glands according to the procedure described above (Table 1). Three of these animals lived until sacrificed at 5, 6, and 7 months respectively after grafting; all had essentially normal blood chemical findings after having gone through a period in which calcium levels were sufficiently low to cause tetany. Eight dogs died of tetany when unobserved during the night (bitten tongues, upset food pans, and distorted positions being considered as evidence of a tetanic death). No deaths occurred during an observed attack of tetany, specific therapy being given when it became obvious that spontaneous recovery would not take place.

As shown on the accompanying chart, a composite of the records of these 11 animals, there was a marked diminution of specific therapy

needed to maintain them free of tetany during the second 2 postoperative weeks as compared with the first 2. It is important to note that the same number of dogs died in each period and that 3 dogs lived through both.

A second group of 12 dogs were operated on, cross-grafts of the parathyroids being performed according to the procedure described above. Five of these dogs lived for over a month postoperatively and one as long as 3 months. In general, these animals showed the same phenomenon of decreasing frequency of specific therapy described above. However, after approximately 3 to 5 weeks there was again a

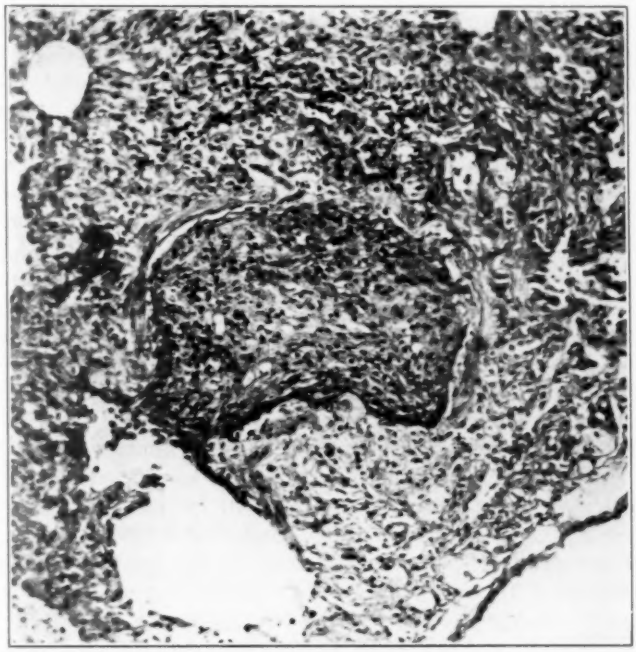

FIG. 1.—Photomicrograph of an embolus at the margin of the lung surrounded by an area of fibrosis. The tissue architecture is not characteristic, but the cellular detail closely resembles that seen in dog parathyroid. (× 150.)

rise in the frequency of therapy until, at the time of their deaths, they needed calcium and parathormone almost daily. Dog 700 can be cited as an example of this type of behavior, for after needing calcium gluconate and parathormone on the 6th and 9th postoperative days, he went $2\frac{1}{2}$ weeks without therapy. On the 4th postoperative day the blood calcium level was 6.5 mg. per 100 cc. and the phosphorus 6 mg. per 100 cc.; on the 13th day, however, the calcium was 7.5 mg. per 100 cc. and the phosphorus 5 mg. per 100 cc. Yet from the 26th day until his death on the 53d day, he needed a total of 12 units of therapy, being given increasingly closer together towards the end of his life. Ten days

before his death in tetany, the calcium level was 5.2 mg. per 100 cc. and the phosphorus level 7 mg. per 100 cc.

There were no evidences in the immediate postoperative periods of the signs or symptoms of pulmonary emboli, or later of pulmonary infarcts. All dogs had careful postmortem examinations of the lungs, heart, and great vessels in an attempt to find the parathyroid emboli. A small mass in the left upper lobe of Dog 620, who died 2 weeks after cross-grafting, proved to be a fibrous tissue plug in a small pulmonary vessel. About the margins of this embolus are cells which microscopically resemble parathyroid cells. Sections of a similar mass in the lungs of Dog 617, sacrificed approximately 6 months after autografting (Fig. 1), showed it to be a cellular mass occluding a pulmonary vessel surrounded by a small area of pulmonary fibrosis. While the architecture of this tissue is not like that seen in normal dog parathyroid, the cellular detail resembles that seen in these glands.

Discussion. In order to be certain that all parathyroids are removed it has been shown that it is necessary to perform complete thyroparathyroidectomies. In 1931 Kunde, Oslund, and Kern[7] temporarily prevented the appearance of tetany in similarly prepared dogs by 75 to 100 gr. (8 to 12 gm.) of thyroid extract daily. Aub and co-workers[1] have demonstrated a definite augmentation of the effects of parathormone in tetany by the administration of thyroid substance. In our experiments we attempted, purely empirically, to establish a somewhat normal thyro-parathyroid relationship by the administration of 1 gr. (6.5 mg.) of thyroid each day. We do not believe this amount was sufficient to delay or prevent the appearance of tetany, nor were the animals myxedematous.

Considering the group of iso-grafted dogs, it appears to us that the phenomenon of decreasing need for therapy associated with a slowly rising calcium and falling phosphorus can be taken as evidence of functioning parathyroid grafts in the lungs. If it had been possible to give these animals 24-hour nursing care, we believe that many of the fatal attacks of tetany could have been aborted and more animals carried to complete recovery. This contention is supported by the fact that the 3 dogs that lived 5, 6 and 7 months on their transplanted glands, lived until sacrificed. Their records are very similar in the early postoperative weeks with those of dogs that died in unobserved attacks of tetany.

The course of the cross-grafted dogs is more difficult to interpret. Most of these animals appeared to be supporting growing grafts for some time when a change in their course occurred, finally ending in a tetanic death. This type of cycle is known to occur in cross skin grafts; and Stone, in discussing immediate cross-grafts of thyroid and parathyroid tissues, felt that involved in this phenomenon was a defense mechanism on the part of the host set in motion by the foreign protein of the graft.

When discussing the possible clinical application of this method of grafting, the effect of these small pulmonary emboli must be considered. In dogs, we can say that they did not give rise to any discernible

deleterious results. Karsner and Ash[6] produced small areas of fibrosis in the lungs of dogs by the injection of turnip and radish seeds into the jugular vein. They do not mention any ill effects suggestive of clinically significant emboli. Norris and Landis,[8] in their textbook on diseases of the chest, mention that small pulmonary emboli pass unnoticed or cause at most "a few days disturbance."

The question of an adequate source of properly prepared and acclimated tissue for cross-grafting is beyond the scope of this report. It is possible that stock tissue cultures grown in pooled human plasma might offer a satisfactory answer. But given such a source, the method herein presented would lend itself to repeated grafting attempts until successful takes were achieved, repeated attempts with only a small degree of operative trauma and an unlimited implantation site.

Summary. A method of achieving intravascular pulmonary grafts is discussed. Experimental evidence in dogs is presented to demonstrate the efficacy of the procedure.

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CARCINOMA OF THE DUODENUM

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From 1927 through 1939, 3 cases of primary duodenal carcinoma were seen at Pondville Hospital. These rare tumors have received considerable discussion in the literature during the last 40 years. The situation is confused, however, by duplication of cases and by the inclusion of examples of carcinoma of the head of the pancreas, the papilla of Vater, the bile ducts, and the gall bladder. Such errors have tended to increase the number of reported cases, particularly in regard to the second portion of the duodenum. Many series of such cases must necessarily be set aside, and even after careful analysis, one cannot be absolutely certain that pancreatic carcinomas or other

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types of malignancies do not enter into the statistical recording. Since the major portion of the work may be devoted to the treatment of cancer, findings from Pondville and similar hospitals are not comparable with those from general hospitals. During the same period that the 3 duodenal carcinomas were seen at Pondville, there were 2 carcinomas of the papilla of Vater among a total of 1654 autopsies. In a similar period, there passed through the laboratory 181 carcinomas of the stomach and 444 carcinomas of the colon and rectum.

Deaver and Ravdin[8] and McGuire and Cornish[30] both reported an incidence of duodenal carcinoma of 0.03% in 151,201 collected autopsies and Eger[11] reported a similar figure in 350,286 collected autopsies. Table 1 shows an analysis of 117,433 autopsies with an incidence of 0.047% for carcinoma of the duodenum.

TABLE 1.—INCIDENCE OF DUODENAL CARCINOMA

Source	No. of autopsies	No. of duodenal carc.
Madyl,[26] Vienna, 1870–1881	20,480	2
Nothnagel,[38] Vienna, 1882–1893	21,358	5
M. Muller,[35] Berne, 1886–1891	5,621	6
Perry and Shaw,[40] Guy's Hosp., 1826–1893	17,652	4
McGlinn,[29] Phila. Gen. Hosp., 1913	9,000	1
Rupp,[48] Zurich, 1912	4,258	1
F. Muller,[34] Basle, 1874–1904	11,314	6
Nickerson and Williams,[37] Boston, 1896–1935	11,206	6
Meyer and Rosenberg,[33] Chicago, 1931	10,876	4
Jetter,[22] Buffalo, 1918–1937	5,668	0
Total	117,433	55 (0.047%)

In estimating the comparative incidence of carcinoma of the large and small bowel in the literature, a number of values are found: Raiford[44] 11.6%, Jefferson[21] 3.1%, Eger[11] 2.7%, Brill[4] and Ewing[13] 2.5%, Mayo[28] 1.4%. Analysis of 152 small intestinal carcinomas gives a percentage incidence of 1.47% (Table 2). What part other malignancies than carcinoma play in reported figures is hard to estimate. Medinger[32] reported 22 cases of malignancies in the small intestines with 30% sarcomas. Raiford[44] analyzed 88 tumors of

TABLE 2.—INCIDENCE OF CARCINOMA OF SMALL INTESTINE IN INTESTINAL CARCINOMA

Source	Carcinoma of small intestines	Total ca. intestines
Madyl[26]	6	100
Nothnagel[38]	11	243
M. Muller[35]	9	41
F. Muller[34]	8	123
Meyer and Rosenberg[33]	10	569
Raiford,[44] 1932	12	304
Nickerson and Williams[37]	8	343
Mayo Clinic,[28] 1907–1939	75	7,775
Stein,[52] 1931–1936	6	259
Jetter[22]	1	133
Pondville series, 1927–1939	6	450
Total	152 (1.47%)	10,340

the small intestines of which 38 were malignant, and 42% of those were carcinomata. If one correlates this fact with the published figures

of Jefferson, Eger, Brill, Ewing, and others, it will be seen that the value of 1.5% applies generally for the incidence of intestinal carcinomas in the small bowel. Including the stomach in the evaluation, the latest Mayo figures[28] report an incidence of 0.57% in the 14,900 cases.

The opinion often quoted, that the jejunum is least frequently the site of carcinoma, appears to have been based on analysis of the earlier reported series. Of 163 reported cases, including the Pondville series (Table 3), carcinoma is found in the duodenum 37%, jejunum 35%, and ileum 28%, showing that the duodenum and jejunum are more likely to undergo carcinomatous changes than the ileum. Sarcoma, on the other hand, most frequently occurs in the ileum.[6,32]

TABLE 3.—INCIDENCE OF CARCINOMA OF SMALL INTESTINE ACCORDING TO LOCALITY

Source	Duodenum	Jejunum	Ileum
Madyl[26]	2	0	4
Nothnagel[38]	5	0	6
F. Muller[34]	6	0	2
Meyer and Rosenberg[33]	4	3	3
Joyce,[23] 1932	1	2	1
Raiford[44]	5	4	3
Nickerson and Williams[37]	6	2	0
Medinger,[32] 1927–1939	3	11	2
Mayo Clinic[25]	23	31	21
Stein[52]	2	2	2
Jetter[22]	0	1	0
Pondville series	3	1	2
Total	60 (37%)	57 (35%)	46 (28%)

The distribution of carcinoma within the duodenum is not so easily analyzed. Dividing the duodenum into 3 parts (1st or preampullary, 2d or periampullary, and 3d or prejejunal), the periampullary region appears to be the most frequent site of carcinoma (Table 4), although there is some question whether, if carcinomas of proven origin in the duodenum alone were used, there would be much difference between the 1st and 2d portions. The 3d portion, however, is undoubtedly less frequently subject to malignant change although scattered cases are reported.[3,9,12,23,27,33,47,50,54]

TABLE 4.—INCIDENCE OF DUODENAL CARCINOMA ACCORDING TO PORTION OF ORIGIN IN DUODENUM

Source	1st portion	2d portion	3d portion
Meyer and Rosenberg[33]	0	3	1
Raiford[44]	2	1	2
Nickerson and Williams[37]	3	3	0
Dewis,[9] 1928	5	5	2
Mayo Clinic,[12] 1925	6	6	3
Mateer and Hartman,[27] 1932	1	4	1
Pic,[41] 1895	2	4	1
Pondville series	1	0	2
Total	20 (34%)	26 (45%)	12 (21%)

Etiology. The causation of carcinoma of the duodenum has been discussed for years without much clarification. Early writers inclined to associate cancer with preëxisting duodenal ulcers. Jefferson[21] col-

lected 30 such cases and after careful evaluation concluded, "that a causal relationship between simple ulcer and carcinoma is difficult to establish in the case of the duodenum." He reported that 99.2% of duodenal ulcers occurred in the 1st portion, which in itself is an argument against such an association. Dewis[9] felt that duodenal carcinoma probably developed independently and that there was little evidence for preëxisting ulcers. Many observers have been misled by the ulcerating nature of the carcinoma itself and it is quite probable that many of the so-called cases are in reality ulcers secondary to the cancer.

Malignant changes in aberrant gastric glands, pancreatic rests, and Brunner's glands have had many old and recent advocates. Bland-Sutton,[2] commenting on these theories, thought that "they belong to the domain of fiction." Robertson[46] has recently reviewed a large number of duodenums and has only twice observed evidence of proliferative activity in Brunner's glands. After reviewing many of the recorded cases of Brunner's gland carcinoma, he concluded that hyperplastic and neoplastic involvements are very rare and that only a few of the reported cases of carcinoma arising from these glands could be accepted without reservations.

The relation of polyps and adenomas to duodenal carcinoma is still controversial. Raiford[44] found adenomas the most common benign tumor in the small intestines, with the highest incidence in the ileum, and thought that they were more susceptible to invasion by carcinoma because of their abnormal arrangement of epithelial lining. Saint[49] reported that 25% of all polypi occurred in the small intestines. In this group, there was only 1 adenoma and that was located in the duodenum. In the large intestines, 36 of 44 polypi were adenomas. Generally, however, most cases of malignancy of the small intestines are not associated with polyposis.[32] Geiser[16] maintained that the duodenal contents chronically irritated a fold of mucosa, producing cancer. Forgue and Chauvin[15] believed that the fixation of the parietal epithelium, the 4 flexures, and the fact that the duodenum was the most widely dilated portion of the intestines were in favor of duodenal carcinoma.

Heggs[20] associated the behavior of pyloric carcinoma, which freely infiltrates the stomach wall but declines to affect the duodenum, with the rarity of duodenal carcinoma. Nagel,[36] however, has shown that this limitation is more apparent than real and cites 48 of 256 compiled cases in which malignancy had macroscopically or microscopically extended beyond the pylorus. Rankin and Mayo[45] have always maintained that the fluid nature, the alkalinity, and the absence of abrupt bends explained the rarity of tumors of the small bowel. Raiford[44] has suggested that, due to the fact that the small intestine developed in the last 4 months of fetal life, it would be plausible to assume that there would be far less opportunity for arrested development and misplaced embryonic tissue than in the remainder of the gastro-intestinal tract.

Pathologic Anatomy. Carcinomas of the duodenum usually occur singly in either a stenosing or polypoid form. Eusterman, Berkman and Swan[12] found 13 stenosing types in their series of 15. Nickerson and Williams[37] found that the stenosing type predominated 3 to 1. The stenosing forms infiltrate into the tissues beneath the mucosa and tend to encircle the lumen. Ulceration and scirrhous replacement are common, causing obstruction by narrowing the lumen. The tumor occurs as an adenocarcinoma or an undifferentiated, medullary carcinoma. Fenwick and Fenwick[14] state that this type is more common in the 3d portion. Extensive carcinoma may occur in the 3d portion, however, without causing obstruction (Case 3). The polypoid type tends to be limited to the mucosa and occurs as a malignant adenoma or a papillary adenocarcinoma. The tumor is composed of large columnar or cylindrical cells with abundant cytoplasm and large, vesicular, hyperchromatic nuclei. Glandular differentiation varies from well-defined glands in the malignant adenomas to a few ill-defined acini in certain types of adenocarcinoma. Mucin may appear either in irregular spaces or in isolated groups of "signet ring cells." Obstruction may occur from blockage of the lumen. Judd[24] felt that this type of growth was more commonly found in the 1st portion.

In 1895, Pic[41] pointed out the difference between carcinoma of the papilla and duodenal carcinoma and noted that the former "as a rule, constitute circumscribed tumors that occupy only a portion of the intestinal wall and consequently resemble, in this respect, carcinomas that are situated in the head of the pancreas itself, whereas, true duodenal carcinoma show the same tendency that is so common in other forms of intestinal carcinoma, namely, to develop in an annular or cylindric manner and so involve the whole circumference of the intestine.

Metastases. Opinions vary on the time and extent of metastases. Generally, the bulk of evidence indicates that they are late and chiefly involve the regional lymph nodes followed more rarely by involvement of the mesentery, liver, lungs, peritoneum, supraclavicular nodes, and bone. Early writers mention metastases to the pancreas; but recent cases fail to substantiate these findings. Nickerson and Williams[37] observed this fact and concluded that "lack of pancreatic metastases emphasizes the necessity of carefully excluding primary carcinoma of the pancreas and that this factor may well explain the variation of incidence noted in other reported series." Craig[7] studied the lymph glands in carcinoma of the small intestines and found 36% eventually metastasized and observed that neither the size of the growth, the duration of symptoms, the size of the nodes, nor the number of palpable nodes was a reliable index of lymphatic involvement.

Signs and Symptoms. Carcinoma of the duodenum occurs approximately 3 times more often in males than females. The average age falls in the 6th decade with reported cases ranging from 17 to 84 years.

In 1899, Aaron[1] wrote, "For therapeutic reasons, the diagnosis of carcinoma of the duodenum should be made as early as possible, a task that requires the keenest medical acumen. In the majority of cases, the tumors are quite large when discovered, for when they are small

we do not get many symptoms so long as the lumen of the intestine is patulous." The truth of this statement still holds today and the problem of diagnosis is still a difficult one. Mayo[28] found, after reviewing 28 cases of carcinoma of the duodenum, that the diagnosis had been actually or tentatively made in 29.2%.

A majority of cases are characterized by a prodromal period of none too characteristic signs or symptoms. The complaints are chiefly referable to the stomach although they are often mistaken for chronic cholecystitis, peptic ulcer, or primary anemia.[3] Vague epigastric distress with occasional attacks of pain, anorexia, weakness, and loss of weight are usually present. Nausea and vomiting may occur, associated with recurrent attacks of intestinal obstruction. There is usually a moderate to marked anemia which frequently will be the only presenting symptom.[18] The anemia may be either macrocytic and hyperchromatic probably due to a failure of absorption of the Hematopoietic Principle of Castle, or microcytic and hypochromic due to blood loss and failure of absorption of iron. Plunkett, Foley and Snell[42] believed that the problem was one of absorption rather than of blood loss. Sowles,[51] on the other hand, thought that there would be no anemia unless ulceration occurred. Both types do occur, although the hypochromic type appears to be more common. In obstructive cases, there is marked alteration in absorption and severe blood loss occurs in the ulcerative type (Case 3). In a number of cases where the lesion has remained small and intact without causing obstruction the blood picture has remained essentially normal.

Occult blood in the stools is a rather consistent finding. The gastric analysis varies with a trend towards low or absent free hydrochloric acid. Cases are reported with hyperacidity.[19] Palpable tumor masses occasionally are reported but generally this sign is uncommon. Jaundice is rare even with involvement of the 2d portion, except in the terminal period. Early writers stressed this sign as characteristic of carcinoma of the 2d portion, and Mateer and Hartman[27] have recently reported its presence in 5 of 6 patients. The Mayo series[12] contrarily notes its absence. With infra-ampullary carcinoma, jaundice is characteristically absent.

As the malignant lesion progresses, many cause obstruction. At this stage, dehydration and toxemia occur as serious complications. McVicar,[31] and Eusterman, Berkman and Swan[12] report cases presenting shock, uremia, and tetany-like manifestations associated with a rise in blood urea, a fall in plasma chlorides, and a rise in the CO_2 combining power of the plasma.

Perforation of duodenal carcinomas is rare, but may abruptly cause the first symptom. Dewis[9] refers to an example of this in the first recorded case of Hambergers in 1746. Ylvisaker[56] recently reported a case of carcinoma of the 3d portion with perforation and formation of a localized abscess.

Occasionally death may occur from erosion of a blood-vessel. Mateer and Hartman[27] reported a case eroding the gastro-duodenal artery and Meyer and Rosenberg[33] an additional case. Case 3 of this

series died following rupture of the first jejunal branch of the superior mesenteric artery.

In the 1st portion of the duodenum, the symptoms simulate those of pyloric carcinoma. In the 2d portion, carcinoma of the duodenum may simulate carcinoma of the ampulla of Vater with jaundice, fever and sepsis. Outerbridge[39] felt that it was unnecessary to separate these groups, although pathologically they were different. In the 3d portion, carcinoma is characterized by bile in the gastric contents providing obstruction has occurred.

Roentgenograms are of increasing aid in the diagnosis of carcinoma of the duodenum, although much less reliable than in other portions of the gastro-intestinal tract. In over one-half of the proved cases, the Roentgen ray evidence has been negative. In Case 3 of this series, the gastro-intestinal series was negative on 4 different occasions with different examiners. Doub and Jones[10] and Raiford[43] list the following findings depending upon the stage of the disease and the amount of deformity and obstruction: (1) Dilatation and vigorous reverse peristalsis in which the tumor has caused obstruction; (2) filling defect more commonly an irregular narrowing but frequently simulating the picture of an ulcer. Harris and Green[17] advise the use of 1 to 3 hour films during a barium examination in order to obtain a full view of the duodenum. Mayo[28] recently reported additional aid in Roentgen ray diagnosis through the use of the Miller-Abbott tube.

Differential Diagnosis. The following conditions must be kept in mind. Malignant and benign pyloric obstruction, carcinoma of the head of the pancreas or gall bladder with involvement of the duodenum, carcinoma of the papilla or terminal portion of the common duct, inflammatory masses, peritoneal tuberculosis, angiomesenteric ileus, and actinomycosis, a rare condition reported by Wheeler.[55]

Prognosis. The average duration of reported case has been from 6 to 14 months. Unless diagnosed and treated early, the mortality is extremely high. Mayo[28] reports 8 cases (12.3%) surviving 5 years. Meyer and Rosenberg[33] refer to 2 cases operated with recovery, and Lundberg[25] and Syme[53] each have reported a case of carcinoma of the 3d portion with operation and recovery.

Case Reports.* Case 1 (Pondville No. 111). A 65 year old male admitted on 10/12/27 with the complaints of epigastric pain and distress of 2 years duration, anorexia, weakness, and 30 pounds weight loss. His pain came on shortly before meals and was relieved by milk and soda. Six months before admission, he had begun noting tarry stools and there had been 1 severe intestinal hemorrhage. Physical examination revealed marked tenderness and spasm over the right rectus muscle above the umbilicus and a severe anemia. Upper gastro-intestinal Roentgen rays revealed the duodenum displaced to the right with a large filling defect in the 1st portion suggesting a chronic indurated ulcer. On 11/2/27, the patient died suddenly from hemorrhage.

Autopsy (partial) revealed a crater-like deformity just below the pylorus. Microscopic section revealed adenocarcinoma.

Diagnosis: Adenocarcinoma of 1st portion of duodenum.

* Cases 1 and 2 were recently included in a report by Ritvo and Hewes: Radiology, 38, 7, 1942

CASE 2 (Pondville No. 16472). An 80 year old male admitted on 11/15/39 complaining of epigastric distress, pains across the lower abdomen, weakness, and 27 pounds weight loss. For 2 months there had been constipation and tarry stools followed by diarrhea 3 weeks before admission. Previous to admission, he had been digitalized for heart disease. Physical examination revealed a marked anemia and a moderately enlarged liver. On 11/18/39, he suffered marked respiratory distress and expired within a few minutes.

Autopsy revealed the distal third of the duodenum almost entirely replaced by a stenosing tumor. The base and margin were indurated and along the floor there was evident thrombosed arteries. There were no metastases. In the lungs, the major branch of the left pulmonary artery, together with smaller right pulmonary arteries, were completely occluded by striated antemortem

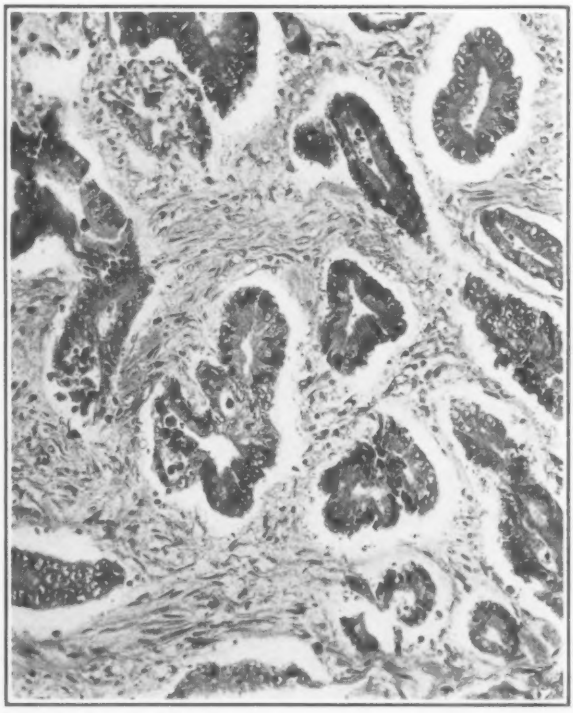

FIG. 1*a*.—Case 2. (× 160.)

clots. Microscopic sections of the duodenal lesion revealed ramifying gland-like structures composed of crowded, acidophilic, cuboidal to cylindrical cells with large hyperchromatic nuclei showing a moderate number of mitoses. In some areas, the tumor cells appear piled up in less differentiated masses. Necrosis was marked (Fig. 1*a* and *b*).

Diagnosis: Adenocarcinoma of 3d portion of duodenum.

CASE 3 (Pondville No. 17235). A 48 year old male admitted 6/1/40. In May 1940, he had been seen outside with the complaints of abdominal pain, nausea, and vomiting of 2 years duration. Two gastro-intestinal Roentgen rays were reported negative. On entering Pondville, he was complaining of mild epigastric pain which came on at night and bore no relation to meals and was not relieved by food. His appetite was good and there was only a suggestive loss of weight. Physical examination revealed marked LUQ muscle

guarding with an associated pain running around the rib margin, a marked anemia (4.7 gm.—30%), stools positive for occult blood, hypoacidity of the gastric contents, and 2 negative gastro-intestinal Roentgen rays. On 6/29/40, the patient had a sudden fainting spell and the following morning he vomited large amounts of blood and a long, firm, blood cast. On 7/2/40, a rigid abdomen was noted and an immediate exploration was performed under local anesthesia by Dr. Donald Hight. The stomach and the 1st and 2d portions of the duodenum were found extending unusually far to the right. Exposure of the 3d portion released a large amount of fecal smelling fluid. The jejunum from the ligament of Treitz for a distance of 12 to 15 inches was gangrenous. The duodenal-jejunal angle was indurated and poorly defined. A Witzel enterostomy was performed in *lieu* of further surgery. The patient failed progressively and died on 7/4/40.

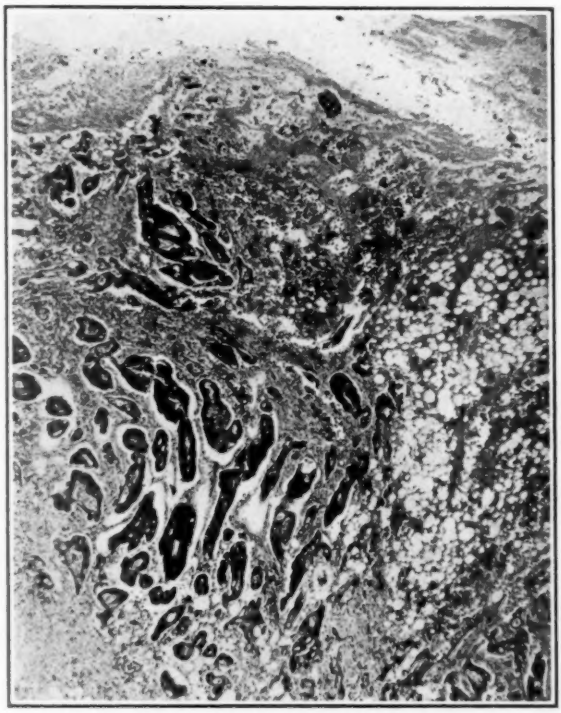

FIG. 1*b*.—Case 2. (× 35.)

Autopsy revealed the 3d portion of the duodenum together with the root of the mesentery, the medial portion of the pancreas, and the transverse colon matted together in a firm, suppurative mass. The duodenal-jejunal flexure was completely destroyed by a necrotic, gray-red, 10 cm. tumor mass which was continuous and indistinguishable from the involved medial portion of the pancreas. The edges of the ulcerating mass were indurated and rolled. The first jejunal branch of the superior mesenteric artery as it crossed the ulcerating mass was completely eroded and thrombosed. The regional nodes were enlarged and firm. Microscopically, sections of the tumor revealed irregular masses of tumor cells and gland-like structures composed of piled up, cuboidal cells with oval, vesicular, hyperchromatic nuclei containing prominent nucleoli and showing a moderate number of mitoses. Necrosis and round cell infiltra-

FIG. 2.—Case 3. (× 35.)

FIG. 3.—Case 3. (× 160.)

tion appeared throughout. All of the lymph nodes were negative for tumor (Figs. 2 and 3).

Diagnosis: Adenocarcinoma of 3d portion of duodenum.

Summary and Conclusions. Three cases of carcinoma of the duodenum are reported including one associated with erosion of the superior mesenteric artery.

In a review of the literature, excluding carcinomas of the pancreas and papilla, 55 carcinomas of the duodenum with an incidence of 0.047% in 117,433 autopsies are recorded. Analyzing 10,340 cases of carcinoma of the intestines an incidence of small intestinal carcinoma is found to be 1.47%. Of 163 cases of carcinoma of the small intestine, involvement of the duodenum is found in 37%, jejunum 35%, and ileum 28% indicating, contrary to frequently quoted opinion, the duodenum and jejunum are more likely to undergo carcinomatous changes than the ileum. In the duodenum carcinoma appears in the 1st portion 34%, 2d portion 45%, and 3d portion 21%.

Carcinomas of the duodenum are generally conceded not to arise from preëxisting ulcers and are seldom associated with polyposis. The location of the duodenum and the nature of its contents explain more satisfactorily the rarity of tumors in this area. When present, these tumors more commonly occur in a stenosing form and less frequently assume a polypoid structure. They metastasize late and usually then only involve adjacent tissues.

A brief summary of signs and symptoms is presented.

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THE PREVENTION OF RENAL PRECIPITATION OF SULFADIAZINE IN DOGS

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PRECIPITATION of the sulfonamides or their acetyl forms in the urinary tract has recently[11] been shown to be one of the most serious complications resulting from therapy with these drugs. As yet, no uniformly successful method for preventing this complication has been reported. Alkalies have been tried, but there is no agreement as to their effectiveness; *e. g.*, Peterson and Finland[9] stated that "Whether renal complications occur more frequently in an acid urine than an alkaline urine has been a subject of more speculation than objective study." It is the purpose of this experimental study to show that precipitation of sulfadiazine and its acetyl form in the urinary tract is a result of their insolubility in acid urine; but in alkaline urine they can be maintained in solution and renal precipitation thereby prevented.

There are numerous reports in the literature showing that sulfapyri-

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dine, sulfathiazole, sulfadiazine, and their acetyl forms are relatively insoluble drugs as compared with sulfanilamide. Curtis and Sobin[2] showed that the solubility of acetyl sulfathiazole is increased in alkaline urine. Sunderman and Pepper[10] showed that the solubility of sulfathiazole and acetyl sulfathiazole is increased in both phosphate buffer and urine in the higher pH ranges. Feinstone[4] found that sulfadiazine was more soluble in urine than water. These investigators also found that urea, glucose, sodium chloride, and high specific gravity did not significantly increase the solubility of these drugs in water or urine. Recently, however, Fox and Rose[5] showed that the solubility of sulfathiazole and sulfadiazine can be increased manyfold by allowing salt formation to occur in alkaline buffer.

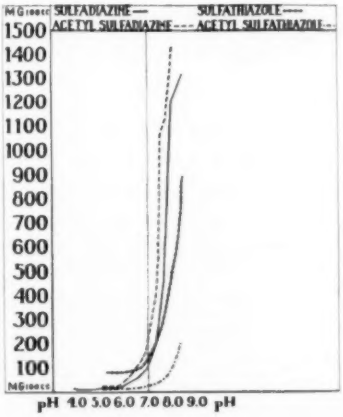

FIG. 1.—The variation in the solubility of sulfadiazine, sulfathiazole, and their acetyl forms in normal human urine from pH 5 to 8.5. *Horizontal axis:* Hydrogen-ion concentration (pH) of the urine at which drug levels were determined. *Vertical axis:* Mg. per 100 cc. concentration of drug in the urine showing the great increase in the solubility of these substances in alkaline urine.

The first step in the prevention of renal precipitation was to determine the solubility of the sulfonamides in urine over the physiologic pH range.[7] As seen in Figure 1, the solubility of these drugs in acid urine below pH 7 is relatively low, but above pH 7, in alkaline urine, the solubility is increased many times.

What is the explanation of this increase in solubility in alkaline urine? The answer lies in the chemistry of these compounds: They are weak acids which ionize and form salts which are relatively soluble.[6] It is this soluble salt formation which increases the solubility of sulfathiazole and sulfadiazine.* The importance of this fact may be realized by comparing the water solubility of these drugs with the urinary solubility (Table 1), and contrasting these findings with the incidence of renal complications.

* Experiments *in vitro* have shown that sulfanilamide has a higher antibacterial potency at pH 7.8 than at pH 6.8.[8]

TABLE 1.—COMPARISON OF WATER AND URINE SOLUBILITY

	Solubility in water at 25° C. (mg./100 cc.)	Solubility in urine at pH 7.4 (mg./100 cc.)	No. of times increase in solubility
Sulfapyridine	37	60	1.6
Sulfathiazole	60	220	3.6
Sulfadiazine	8	280	35.0
Sulfanilamide	1000	1700	1.7

Sulfanilamide is the most soluble in both water and urine, and the solubility of this drug and its acetyl form is well in excess of the urinary levels obtained during therapy; there are few, if any, instances of its renal precipitation.

Sulfapyridine represents the other extreme in that it is relatively insoluble in water, and its urinary solubility is only slightly increased by ionization; accordingly, in urine it is the least soluble of all the drugs, and alkaline therapy can improve this but slightly (Table 1). It is generally agreed that therapy with this drug produces the highest incidence of renal obstruction.

Sulfadiazine is the least soluble in water, but its solubility is increased over 30 times in urine at pH 7.4 as a result of ionization. At this pH, sulfadiazine has a higher urinary solubility than the other sulfonamides except sulfanilamide; but at pH 6.5, its solubility is the lowest.

Sulfathiazole has a higher water solubility than sulfadiazine, but the increase in its solubility by ionization is much less (3.6 times); consequently, its solubility in urine at pH 7.4 is also less.

The acetyl derivatives likewise can ionize to form soluble salts. Acetyl sulfapyridine, however, ionizes only slightly, and accordingly, its very low water solubility is but scarcely increased within the physiologic pH range (30 mg. at pH 8). Acetyl sulfathiazole is even less soluble in water (7 mg.), but this is increased considerably by ionization, as seen in Figure 1 (60 mg. at pH 8). Acetyl sulfadiazine differs from the others in that it is slightly more soluble than the free form (15 cf 12 mg. at 37° C.), and it is more extensively ionized than any of the drugs including the free form so that at pH 7.5 a concentration of 1000 mg. may be obtained.

The solubility of the sulfonamides may be summarized as follows: Sulfanilamide and its acetyl form, although only slightly ionized within the physiologic pH range, are relatively soluble in both water and urine. Sulfapyridine and its acetyl form, relatively insoluble in water, are very slightly ionized, and remain very poorly soluble in urine. Sulfathiazole, sulfadiazine, and their acetyl forms are also relatively insoluble in water, but their high degree of ionization and salt formation increases many times their solubility in urine above pH 7.

From a practical point, it seems important to determine whether precipitation of sulfadiazine might occur when the urine is acid, and might be prevented when the urine is alkaline. Experiments were then conducted on dogs to determine whether it is possible by the administration of sodium bicarbonate to raise the urinary pH and thereby increase the ionization (and solubility) of sulfadiazine suffi-

ciently to prevent its precipitation in the urinary tract. This was compared with the results obtained in acid urine when ammonium chloride was administered. These experiments were conducted in three parts, as follows:

Experiment A. Ammonium chloride and sodium bicarbonate were administered orally with sulfadiazine to determine the effect of acids and alkalies on drug excretion and crystalluria.

Experiment B. Sodium bicarbonate was administered with powdered and enteric coated sodium sulfadiazine to compare the effect of alkalies on gastro-intestinal absorption and urinary excretion.

Experiment C. Sulfadiazine was given subcutaneously to eliminate variations due to gastro-intestinal absorption: Sodium bicarbonate and ammonium chloride were administered by mouth.

EXPERIMENT A. The renal excretion of sulfadiazine in relation to urinary pH.

Method. Sulfadiazine* (0.2 gm. per kilo of body weight) was administered by mouth daily for 44 days to two normal dogs. During the first 14 days sulfadiazine alone was given (control period). For the next 6 days equal amounts of sulfadiazine and sodium bicarbonate were given (alkali period). For the next 7 days they received 0.5 gm. enteric coated ammonium chloride in addition to the sulfadiazine (acid period). Finally, they were given equal doses of sulfadiazine and sodium bicarbonate for the last 11 days. All drugs were administered in fresh chopped meat. The fluid intake (unrestricted) was recorded for each 24 hour period. The dogs remained in metabolism cages throughout the entire experiment. Blood sulfadiazine levels were done twice weekly. Urine specimens were collected as voided during the day, and toluol was added to the collecting flasks for the overnight specimens. The quantity, specific gravity, pH and sulfadiazine level of each urine specimen was determined.† The pH was measured with the Beckman glass electrode pH meter. The sulfadiazine levels were determined by a modification of the Bratton-Marshall method[1] using a Klett-Summerson photoelectric colorimeter with a No. 54 filter. The sulfadiazine levels were done in duplicate and checked within 2%. The majority of determinations checked within 1%.

From this data the daily excretion was determined, and the average percentage of sulfadiazine excreted in 24 hours was computed.

Results. (*a*) The pH of the urine was raised during the sodium bicarbonate period and lowered during the ammonium chloride period. The "average" urinary pH during the three periods was as follows:

	Male (pH)	Female (pH)
Control	6.52	7.04
Sodium bicarbonate	7.19	7.25
Ammonium chloride	6.05	6.16

(*b*) The urinary sulfadiazine levels fluctuated with the changes in urinary pH induced by the two adjuvant drugs employed (Fig. 4).

(*c*) Twenty-four hour urinary excretion of sulfadiazine varied directly with the pH (Fig. 3, Table 2).

(*d*) During the ammonium chloride period, crystals of sulfadiazine were present in the urine of both dogs. At this stage of the experi-

* The sulfadiazine used in these experiments was supplied by Lederle Laboratories and E. R. Squibb & Sons.

† Since dogs do not acetylate the sulfonamides,[3] this determination was unnecessary.

ment a quantitative method for measuring the amount of solid drug not in solution was devised[7] and conducted as follows: 50 cc. of each specimen of urine was centrifuged, and a sulfadiazine determination was done on 1 cc. of the supernatant and on 1 cc. of the sediment. In a number of instances a significant difference between the two determinations was encountered, indicating the presence of large amounts of solid drug in the urine which was not in solution and which was thrown down by centrifugation.

TABLE 2.—THE EFFECT OF SODIUM BICARBONATE AND AMMONIUM CHLORIDE ON THE DAILY RENAL EXCRETION OF SULFADIAZINE BY DOGS RECEIVING CONSTANT DOSAGE OF DRUG

	Average daily excretion of sulfadiazine				Average increase + or decrease − from control period			
	Grams		Per cent		Grams		Per cent	
	M	F	M	F	M	F	M	F
Control	1.29	1.15	40.3	60.5				
Sodium bicarbonate	2.04	1.39	63.9	73.1	+ .75	+ .24	+58	+21
Ammonium chloride	0.85	0.73	26.5	38.4	− .45	− .42	−35	−36

Dosage: 0.2 gm. sodium bicarbonate per kilogram body weight; male, 3.20 gm.; female, 1.99 gm.

(*e*) Both dogs were then given sodium bicarbonate again, and with the rise in urinary pH, the undissolved sulfadiazine in the urine disappeared, and the supernatant and sediment levels approximated one another. The urinary sulfadiazine levels again exceeded those obtained during the control and ammonium chloride periods.

(*f*) Blood sulfadiazine levels averaged 30.8 mg. for the male, and 15.6 mg. for the female. The blood levels did not vary significantly from one period to the next.

Comment. The increase in solubility of sulfadiazine above pH 7 is a result of increased ionization with formation of soluble salts. If the pH of the urine remains above 7, the solubility is increased and the likelihood of renal precipitation is diminished.

Figure 2 shows the pH and mg. level of each individual specimen of urine throughout the entire experiment. It will be noted that in acid urines (below pH 7), the urinary drug levels are considerably lower than those in alkaline urines (above pH 7). Furthermore, many of the levels above 200 mg. in specimens below pH 7 are false levels; *i. e.*, during the ammonium chloride period there was solid drug in the urine, and these concentrations do not represent sulfadiazine in solution (encircled points, Fig. 2). This is most marked in the male. The pH of the female urine was consistently higher than the pH of the male urine. Likewise, the per cent of drug excreted per day by the female was higher, and the amount of solid drug in the female urine was consistently less.

There is a close correlation between the effect *in vitro* of pH on drug solubility and the results of these experiments. When an average line is drawn through the concentration points (Fig. 2), the resulting curve is similar to the *in vitro* solubility curve (Fig. 1). In both dogs the solid drug disappeared when the pH of the urine exceeded 7. There are several exceptions to this. In Figure 2 the dots with the circles

represent specimens in which there was considerable solid drug. In the male there are 4 specimens above pH 7 which contained solid drug. If reference is made to Figure 1, it will be seen that the concentration of drug in 3 of these exceeds the solubility limits of sulfadiazine. This is further confirmation of the relation between pH, urinary levels, and renal precipitation.

The purpose of Experiment B is to determine whether the oral administration of sodium sulfadiazine will maintain a higher urinary pH than is obtained with sulfadiazine, and thereby avoid renal precipitation.

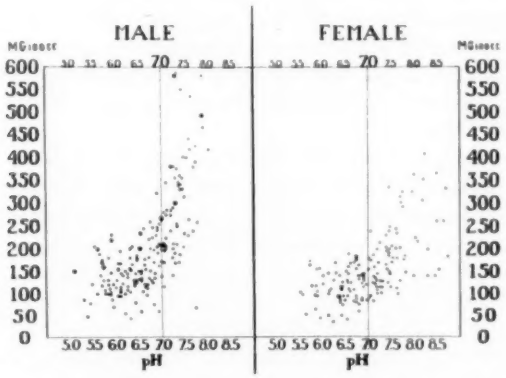

FIG. 2.—The occurrence of crystalluria in relation to the pH and drug concentration of the voided urine. *Horizontal axis:* The pH of the freshly voided urine. *Vertical axis:* Sulfadiazine level in mg. of each specimen. Encircled points represent specimens containing solid drug.

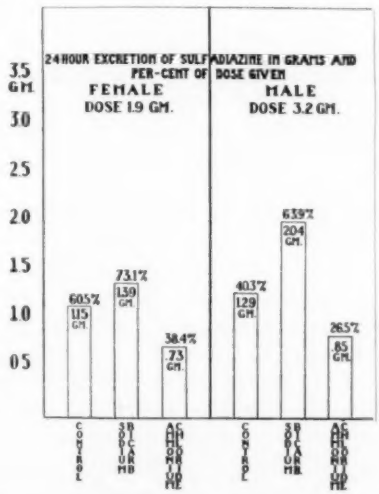

FIG. 3.—The effect of sodium bicarbonate and ammonium chloride on the daily renal excretion of sulfadiazine by dogs receiving constant dosage of drug.

EXPERIMENT B. *Method.* Sodium sulfadiazine was given orally in equimolar doses corresponding to the dose of sulfadiazine given in Experiment A.

The same two dogs were used in this experiment. Following a control period (sodium sulfadiazine only) lasting 9 days, they were given sodium bicarbonate for 10 days, but in smaller doses so that the total quantity of sodium given was equal to that in Experiment A.

This experiment was then repeated using enteric coated sodium sulfadiazine to avoid precipitation of free sulfadiazine by the hydrochloric acid in the stomach. The same routine of blood and urine analyses were employed as in Experiment A.

Results. (*a*) The pH values of the individual urine rspecimens were approximately the same with enteric coated sodium sulfadiazine as with the powdered sodium sulfadiazine and were no higher than during the administration of free sulfadiazine alone. When sodium bicarbonate was administered so that the total quantity of sodium (including sodium sulfadiazine) equaled the amount of sodium given as bicarbonate with the free sulfadiazine, there was the same rise in urinary pH as described in Experiment A.

(*b*) The urinary sulfadiazine levels during the sodium bicarbonate period again exceeded those obtained during the control period.

(*c*) Crystals of drug were found in only one urine specimen throughout this experiment, and in this instance only was there a significant variation between the supernatant and sediment determinations.

(*d*) Twenty-four hour urinary excretion of sodium sulfadiazine, either powder or enteric coated, was similar to the results obtained with the free drug. The increased drug excretion with the additional sodium ion was also similar.

	Male		Female	
	average daily excretion Dose 3.21 gm. (sulfadiazine)		average daily excretion Dose 1.83 gm. (sulfadiazine)	
	Grams	Per cent	Grams	Per cent
Control	1.35 (1.35)*	42.4 (42.3)	0.82 (1.06)	44.3 (55.5)
Sodium bicarbonate	1.88 (1.82)	58.5 (57.0)	1.20 (1.15)	64.9 (60.2)

* Figures in parentheses are values obtained with powdered sodium sulfadiazine.

(*e*) Blood sulfadiazine levels averaged 24.8 mg. for the male, and 15.7 mg. for the female. Again, there were no significant variations from one period to the next.

Comment. Sodium sulfadiazine is presumably converted to sulfadiazine in the acid contents of the stomach. The purpose, therefore, of giving the enteric coated sodium sulfadiazine was to eliminate this conversion in the stomach. It has, however, been shown that the small intestinal contents are also acid,[3] so that prior to absorption, most of the salt is changed to the acid form, regardless of the enteric coating. At the time of absorption, or just afterwards, the drug is in the alkaline environment of the blood (pH 7.4) and almost completely ionized.[5]

Since the alkali or acid therapy might have influenced gastro-intestinal absorption of sulfadiazine and secondarily altered the rate of excretion, it was decided to administer the drug subcutaneously to eliminate this factor in the following experiment.

When sodium sulfadiazine (0.2 gm. per kilo) was given subcutaneously, the urinary levels were far in excess of the levels obtained by

oral administration, and the blood levels were also higher (better absorption). As there was considerable solid drug not in solution in the urine, it was necessary to reduce the dose by half to 0.1 gm. per kilo.

EXPERIMENT C. *Method.* Two normal dogs were given 0.109 gm. sodium sulfadiazine (equivalent to 0.1 gm. sulfadiazine) per kilo of body weight, by injecting a 5.6% solution into the region of the shoulders.* The male dog received 32 cc.; the female, 18.5 cc. each day for 30 days. This experiment was again divided into three periods: a control, a sodium bicarbonate, and an ammonium chloride period, each lasting 10 days. The sodium bicarbonate and ammonium chloride were administered by mouth, as in the previous experiments.

In addition to the routine blood and urine analyses employed in Experiment A, specimens of blood were collected under oil at various intervals throughout the three periods for pH measurement.

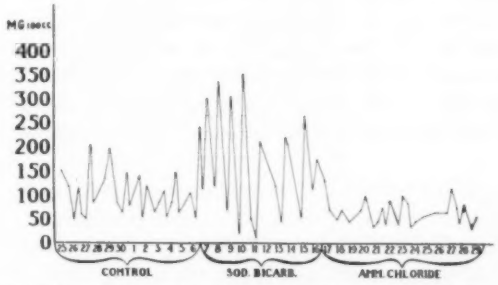

FIG. 4.—The variations in the urinary concentration of sulfadiazine with adjuvant therapy. (The same dose of sulfadiazine was administered throughout the three periods. Crystals of sulfadiazine were abundant during the ammonium chloride period and were rare during the sodium bicarbonate period. The same results were obtained when the drug was given orally or subcutaneously.)

Results. The urinary sulfadiazine levels were again elevated during the sodium bicarbonate period, and depressed during the ammonium chloride period (Fig. 4).

(*b*) The "average" urinary pH is shown in the following table:

	Male (pH)	Female (pH)
Control	6.28	7.19
Sodium bicarbonate	7.12	7.83
Ammonium chloride	6.17	6.95

(*c*) Twenty-four hour urinary excretion of subcutaneously administered sodium sulfadiazine:

	Male		Female	
	Dose 1.66 gm. (sulfadiazine) average daily excretion		Dose .96 gm. (sulfadiazine) average daily excretion	
	Grams	Per cent	Grams	Per cent
Control	1.09	65.5	.82	85.2
Sodium bicarbonate	1.28	77.1	.79	82.1
Ammonium chloride	0.89	53.6	.55	57.3

* There was no evidence of infection or irritation in the subcutaneous tissues during the 30-day period. There was only slight induration of the tissue at the sites of injection.

(*d*) The variation in the pH of the blood specimens during the three periods did not exceed 0.06. The highest pH was 7.25, the lowest 7.19.

(*e*) Blood sulfonamide levels averaged 15.8 mg. for the male, and 11.7 mg. for the female. There were no significant variations in blood levels during the three periods.

Comment. During the three periods there was no significant change in blood pH, and presumably the rate of absorption of sulfadiazine from the subcutaneous tissues remained constant. There was, however, the same increase in sulfadiazine concentration in the urine during the sodium bicarbonate period, and decrease during the ammonium chloride period (Fig. 4) as seen in the experiments with oral administration of the drug.

The drug output of the male dog, as in previous experiments, increased during alkali therapy, and decreased during acid therapy. This was also true for the female, except that the control pH was high (7.19), and at this pH the solubility of sulfadiazine is above the concentration obtained in the urine specimens in this experiment. Accordingly, during the alkali period, although both pH and drug level increased, the 24 hour excretion did not, partly because of diminished fluid intake.

Discussion. Alkali therapy was originally used with sulfanilamide to combat acidoses; but subsequently this was discontinued. When sulfapyridine was introduced, renal obstruction was frequently encountered, and alkalies were again administered in an effort to prevent this complication. Alkalies do not prevent precipitation of sulfapyridine, since they increase its solubility but slightly.[2] The solubility of sulfathiazole and sulfadiazine, on the other hand, is greatly increased by alkali therapy provided the urinary pH is maintained above pH 7. To accomplish this, sufficient alkali is required to neutralize the acidity of sulfadiazine itself in addition to the urinary acidity.

Why does one patient receiving sulfadiazine have renal precipitation of the drug, and another patient receiving the same dosage have no evidence of renal obstruction? Since there is a wide (individual) variation in the pH of urine, it seems logical that the person with a consistently acid urine would be the most likely to precipitate the drug in the kidneys.

These relationships are particularly essential when large doses of drugs are given. For example, if a patient absorbs 6 gm. of sulfadiazine per day and has an average daily output of 1500 cc. of urine, it would require an average urinary level of 400 mg. to excrete the total quantity in 24 hours. Doubling the daily output of urine might halve the urinary sulfonamide concentration, but this level would still be far in excess of the solubility of the drug, and a pH above 7 (preferably 7.5) would be needed to insure solution.

The administration of acids or alkalies during sulfadiazine therapy changed the quantity of drug excreted regardless of the mode of administration. When the drug was given by the subcutaneous route, there was the same increase in excretion during alkali therapy and decrease in excretion during acid therapy as occurred when sulfadiazine was given

orally. This would indicate that acid and alkali therapy do not alter the extent of absorption of sulfadiazine from the gastro-intestinal tract but alter the rate of excretion (and reabsorption) by the kidney.

There was no correlation between specific gravity and drug excretion. Low specific gravities were obtained with high urinary concentration levels and *vice versa*. The specific gravity of specimens containing solid drug not in solution were evenly distributed from 1008 to 1030.

Summary. The effect of pH on the solubility of sulfadiazine has been demonstrated *in vitro* and *in vivo* in these experiments. Insoluble sulfadiazine becomes relatively soluble as salt formation is induced by raising the urinary pH (Fig. 1).

Experiments in dogs showed that when the pH of the urine exceeds 7, crystalluria is minimal, higher urinary concentrations of drug are obtained, and the total quantity of drug excreted is likewise higher (Fig. 2). Conversely, during acid therapy, when the urinary pH was below 7, crystalluria was marked, urinary levels were low, and the total quantity of drug excreted was considerably less.

A comparison of the pH and sulfadiazine levels in the urine specimens of dogs under therapy gave a curve (Fig. 2) that closely simulates the *in vitro* solubility curve (Fig. 1).

The subcutaneous administration of sulfadiazine (Experiment C) increased considerably the degree of absorption of sulfadiazine so that smaller doses had to be used. Following the administration of sodium bicarbonate, there was the same increase in urinary pH and urinary sulfonamide concentration as occurred with the oral administration of sulfadiazine. Acid therapy lowered the pH and reduced the urinary sulfadiazine concentration and total drug excretion.

It has been shown in these experiments that raising the urinary pH above 7 by the use of sodium bicarbonate is effective in increasing the solubility of sulfadiazine and preventing its precipitation in the kidneys of dogs. This increased solubility of sulfadiazine in alkaline solutions further suggests a method of treatment of renal obstruction resulting from the precipitation of the sulfonamides. In the ureteral and pelvic lavage therapy of sulfonamide renal obstruction, alkaline bicarbonate or carbonate solutions are recommended, since these will dissolve drug crystals much better than warm water or normal saline solution. These methods of prophylaxis and treatment are under clinical trial.

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CLINICAL AND EPIDEMIOLOGICAL FEATURES OF AN OUTBREAK OF PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN ETIOLOGY AMONG HOSPITAL AND MEDICAL SCHOOL PERSONNEL

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When an epidemic of primary atypical pneumonia abruptly involved the student body and staff of the University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital, it was realized that this outbreak among a closed group of known clinical and roentgenographic background afforded an unusual opportunity to investigate this malady. Accordingly, the earliest sign of illness was considered adequate reason for hospitalization. In each case repeated bedside observations and laboratory studies were made in an effort to learn more about these aspects of this disease. The purpose of this paper is (1) to report the clinical findings in 40 cases from the institutional personnel who were hospitalized with definite roentgenographic evidence of pneumonia between August 1 and September 30, 1942; and (2) to present the results of epidemiologic studies of a slightly larger group of patients and 1587 contacts. The epidemiologic investigations were carried out with the following objectives: (*a*) to compare the chronologic distribution of cases among institutional personnel with that among other persons in the community admitted to the same hospital; (*b*) to determine, if possible, the explanation for any significant differences in the incidence of the disease in various subdivisions of the institutional personnel; (*c*) to evaluate the contagiousness of the disease; (*d*) to determine whether the chief means of spread of the disease was through clinically recognizable cases or through subclinical cases and carriers.

Clinical Features. The age distribution of patients in this series was restricted; all but 3 were between 19 and 30 years of age; the oldest was 49. There were 32 males and 8 females, nearly all of whom were previously in good health. The relative homogeneity of this group of patients and the circumscribed nature of the outbreak make it apparent

that a single etiologic agent was responsible for virtually all of the cases. The clinical features for the most part resembled those described by others.[3,4,6,9–12,14,15]* There were no fatalities.

Symptoms. In most instances, the onset was insidious with prodromal symptoms of malaise, generalized aching and sore throat lasting 1 to 7 days. Because sore throat and aching appeared very commonly at an early stage of the disease, persons with these symptoms were regarded with great suspicion during the epidemic, whereas those with simple coryza were thought to be much less liable to develop atypical pneumonia. The acute phase of the illness in half the cases began with chilly sensations, but only 3 had frank, shaking chills. Every patient soon developed a persistent cough which was very disturbing and was relieved neither by cough mixtures nor by steam inhalations. Although the most severely ill patients suffered considerable dyspnea during the stage of maximum pulmonary involvement, and especially after severe paroxysms of coughing, this was noted later in the course of the illness and was less prominent than in comparable cases of pneumococcal pneumonia. This might also be said for cyanosis in these same patients, although cyanosis was more prominent than indicated in reports of other outbreaks of this same type of illness. Although pleural pain was suffered by only 1 patient, half of the patients complained of severe substernal pain which was thought to originate in the trachea because the onset coincided with that of the cough. The more frequently encountered symptoms are listed in Table 1.

TABLE 1.—INCIDENCE OF SYMPTOMS IN 40 PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA

Symptom	No. patients
Cough	40
Headache	33
Generalized aching	33
Sore throat	30
Backache	25
Chilliness	21
Tracheal pain	20
Eye pain	14
Dyspnea	12
Coryza	9
Mental confusion	4
Pleural pain	1

Signs. In many cases, a relative bradycardia was recorded but in the more severely ill patients tachycardia developed just before or during the period of lysis. The respiratory rate was significantly increased only in the cases with extensive pulmonary involvement and those complicated by asthma or wheezing. The temperature charts showed wide variations depending upon the severity of the case, but in general, the fever records can be placed in 3 groups: (1) Twenty patients with considerable pulmonary involvement and prostration had fluctuating fever for from 5 to 11 days with daily peaks of 39° to 41° C.

* Since the literature on primary atypical pneumonia has recently been reviewed by Dingle and Finland,[3] references given in this paper are limited to those which are specifically related to the contents of this report.

in the afternoon or evening; this was followed by lysis over a period ranging from 2 to 4 days. (2) Thirteen moderately ill patients had a similar type of fever for less than 5 days. (3) The 7 mild cases had only a slight remittent fever for 1 to 8 days. None of the patients included in this study had a sustained high plateau of fever and none developed herpes labialis simplex, but herpes has been noted in 2 of 4 more recent cases with relatively prolonged high fever. Once the temperature had fallen for a day or more, there was very seldom any secondary rise such as that reported by Longcope.[11]

Slight cervical lymph node enlargement was noted in several patients during convalescence. The only patient with a palpable spleen was a medical student known to have congenital hemolytic jaundice. Although Kneeland and Smetana[9] have reported arthritis, dermatitis, pericarditis and jaundice in severely ill patients, none of these extrapulmonary findings was noted in the group under consideration.

Chest findings on admission were usually minimal or absent even though there was definite evidence of pneumonia by Roentgen ray. Most frequently the earliest signs were slight dullness and fine, dry râles late in inhalation or only post-tussively. Just before or during the period of lysis and clinical improvement râles became more moist and abundant and far more widespread, but tubular breathing was seldom heard. In general, the chest signs and Roentgen ray findings were very similar to those described by others.[3,4,6,9–12,14,15] The distribution of pulmonary lesions according to lobes (Table 2) was much the same as is seen in pneumococcic pneumonia. This similarity has also been noted by Dingle *et al.*[4]

TABLE 2.—LOCATION OF PULMONARY LESION IN 40 PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA AS DEMONSTRATED BY PHYSICAL SIGNS AND ROENTGENOGRAPHS

Lobe involved	No. cases
Right lower	11
Right middle	1
Right upper	2
Left lower	12
Left upper	2
Right lower and left lower	8
Other combinations	4
Total	40

Pleural effusion was suspected in 4 cases by physical signs and in 3 of these by Roentgen ray, but was proven in only one case by thoracentesis with removal of clear, yellow fluid which was bacteriologically sterile.

Roentgenographic Findings. The earliest change in the chest roentgenograph was a prominence of basal bronchovascular markings extending from the hilus as a fan-shaped shadow. Often this change was appreciated only by comparison with previous films which were available in nearly every case. Homogeneous shadows of low density were later superimposed upon these linear markings. Extension of the fan-shaped density toward the periphery was noted next, and in the more severe infections there was a mottled bronchopneumonic type of

infiltration. The resemblance to the Roentgen ray picture of pulmonary tuberculosis was sometimes striking. Actually at the time of maximal roentgenographic change, the patient had already begun to improve clinically.

In some cases the initial Roentgen ray finding was a basal shadow of considerable density which was not unlike that seen in pneumococcal pneumonia.

Asthma. Asthmatic wheezes were noted in 15 cases during the stage of resolution. One patient was convalescing from a mild attack of the disease when he was exposed to ragweed pollen and developed severe asthma, followed by a serious exacerbation of pneumonia. He was the only one who had suffered from asthma during previous ragweed seasons. Another patient had moderately severe asthma for several days. The remaining 13 patients had definite wheezing and prolongation of expiration with some degree of respiratory difficulty. Of the 40 persons under consideration, 10 gave a history of previous allergic disease (asthma, allergic rhinitis, hives or migraine). It is statistically significant that 8 of these 10 persons developed asthma or wheezing during the stage of resolution, whereas of the 30 patients with negative allergic histories, only 7 developed wheezing. Kneeland and Smetana[9] and Longcope[11] have also noted obstructive or asthmatic type of breathing but have not commented upon it from the standpoint of allergy. Its exact significance remains to be determined by further observations.

Laboratory Findings. *Sputum* was scanty and thin in the early stages of the disease but later it usually became grayish green, mucoid and more abundant. Blood streaking was noted only after paroxysms of coughing in severely ill patients. On the basis of the pathologic findings in the lungs of the few fatal cases of this disease, one might expect the sputum to be laden with mononuclear leukocytes, but actually the cellular content varied greatly. Some sputum smears showed a predominance of polymorphonuclear leukocytes; in others, mononuclear cells were more abundant and in still others, the two types of cells were equally divided. No correlation between the stage of the disease and the cellular content of the sputum could be established.

Bacteriologic Studies. Smears of sputum stained by the Ziehl-Neelsen technique were prepared at least once in each case but no acid-fast bacilli were found.

Cultures of sputum usually showed diphtheroids, *Neisseria catarrhalis*, *Streptococcus viridans*, *Hemophilus influenzæ*, *Staphylococcus aureus* and *Staphylococcus albus*. In a few instances pneumococci of the higher types were isolated by mouse inoculation but they were never present in great numbers on rabbit's blood agar plates inoculated with sputum. Repeated cultures of sputum failed to reveal any convincing evidence of secondary bacterial invasion in this disease, but 3 patients had many colonies of beta-hemolytic streptococci in their throat cultures late in the acute phase of their illness.

Blood cultures were obtained 1 to 4 times from every case and all were negative.

Isolation of a virus from sputum, nasal washings and stools by serial passage through mice and chick embryos was attempted without success.

Immunologic Studies. Blood serum was collected from many of the patients on admission and again at 1 month after the onset of illness. These specimens are to be tested for antibodies against a number of the viruses known to cause respiratory infection in man and in some animals. Thus far, 26 convalescent sera have been tested by complement fixation for *Rickettsia burneti* with negative results.*

Sheep-cell Agglutination. Fifteen admission specimens and 19 convalescent specimens were tested for sheep-cell agglutination. The technique consisted of mixing 0.5 ml. of serial dilutions of inactivated serum with 0.5 ml. of a 2% suspension of washed sheep cells, after which 1 ml. physiologic saline solution was added to each tube to bring the total volume up to 2 ml. After the tubes had incubated at 37° C. for 2 hours, they were placed in a refrigerator at 4° C. and read the following morning. The results as shown in Table 3 are inconclusive, especially when one considers the sheep-cell agglutination titers reported for normal human serum.[2] However, the fact that 1 patient, whose serum was negative on admission, developed during convalescence a titer of 1:64 and another a titer of 1:512 may be significant. In neither of these cases was the blood picture suggestive of infectious mononucleosis. Altogether 5 of 11 patients whose admission sera were negative developed sheep-cell agglutinins during convalescence.

TABLE 3.—RESULTS OF TESTS FOR SHEEP CELL AGGLUTININS IN PATIENTS' SERA TESTED ON ADMISSION AND DURING CONVALESCENCE

Titer* on admission	No. sera	Titer* of corresponding sera when tested 25 to 40 days after onset of illness					
		Negative	1:8	1:16	1:32	1:64	1:512
Not tested	4	0	1	2	1	0	0
Negative	11	6	0	2	1	1	1
1:8	3	2	1	0	0	0	0
1:16	1	0	0	1	0	0	0
Totals	19	8	2	5	2	1	1

* Titers are expressed in terms of final dilution of serum after addition of sheep cell suspension and saline.

Leukocyte Response. The white blood cell counts recorded on the day of admission to the hospital are shown in Table 4. During the early part of their illness, most of the patients had a white blood count within or near the normal range. During or soon after the period of lysis, 11 of the most severely ill patients developed a leukocytosis ranging from 12,000 to 20,000 cells per c.mm., and in more recent cases counts as high as 25,000 have been recorded at this stage of the disease.

* The complement-fixation tests with *Rickettsia burneti* were performed by Dr. Ida A. Bengtson, Senior Bacteriologist, and reported through Dr. Charles Armstrong, Chief of the Division of Infectious Diseases, National Institute of Health, Bethesda, Md.

In the majority of instances, a slight neutrophilia and shift to the left were noted whenever there was an appreciable leukocytosis. Monocytosis of 10 to 25% was recorded in 11 cases on admission and another patient had 25% monocytes in her blood smear during the early phase of convalescence. At various stages of the disease, an eosinophilia of 5 to 11% was noted in 8 cases. These differential white blood cell counts were made by a number of persons and only 100 cells were counted in each smear. The errors, both technical and unavoidable[1] in such counts are acknowledged.

TABLE 4.—TOTAL WHITE BLOOD CELL COUNTS IN 40 CASES OF PRIMARY ATYPICAL PNEUMONIA ON DAY OF ADMISSION TO THE HOSPITAL

White blood cells per c.mm.	No. patients in given range
3,000– 6,000	6
6,000– 9,000	18
9,000–12,000	11
12,000–15,000	5

Therapy. Treatment in all cases was largely symptomatic. Sulfadiazine was given to 16 patients at various stages of the disease but did not appear to alter the course of the illness.

Eight patients were given plasma (100 to 300 cc.) or whole blood (300 to 900 cc.) withdrawn from persons during the first 2 to 4 weeks of their convalescence from the same type of illness. Since September 30, 4 more patients have been similarly treated. It is obviously impossible to evaluate the results of such treatment in this small group. It appeared, however, that no specific effect could be demonstrated.

Oxygen was administered to 8 patients by tent or mask for varying periods of time with considerable relief of cyanosis and dyspnea. Most of the seriously ill patients were provided with special nursing care which proved very helpful during the height of their illness. Adrenalin was necessary in the few severe cases of asthma which did not respond to ephedrine. As mentioned previously, steam inhalations and cough mixtures were for the most part ineffective, but when sputum production became abundant, postural drainage appeared to be beneficial in some instances. It was felt that a high vitamin, high caloric diet shortened convalescence. This was given as soon as tolerated because considerable weight was lost by most of the patients. Fluids were forced to 3500 ml. *per diem.* and in some cases 4 to 8 gm. of extra salt were added to the diet each day.

TABLE 5.—DURATION OF HOSPITAL STAY IN 40 CASES OF PRIMARY ATYPICAL PNEUMONIA

Days hospitalization	No. patients in given period
5 or less	2
6 to 10	11
11 to 15	13
16 to 34	14

Convalescence. An indication of the duration of illness is given by a tabulation of the length of hospital stay.

The days from work lost by 39 patients* with pneumonia totaled approximately 1000. (These included the days lost prior to admission to the hospital.) The average interval from admission to the date of return to work was 23 days. The period of convalescence averaged 17 days as measured from the termination of fever to the resumption of active duties. It should be pointed out, however, that some of the patients had a very mild attack of the disease, and that some of the most severely ill patients started back to work on a part-time basis. A better concept of extent of convalescence can be obtained from Table 6.

TABLE 6.—DURATION OF CONVALESCENCE IN 39 CASES† OF PRIMARY ATYPICAL PNEUMONIA

Length of convalescence	No. patients† in given period
10 days or less	4
11 to 15 days	18
16 to 20 days	8
21 to 41 days	9

During convalescence, 12 persons suffered varying degrees of mental depression lasting from 3 to 21 days, or an average of 12 days. Throughout the early part of convalescence, all but 2 of the 40 patients complained of marked asthenia and easy fatigability which was considered more severe than that ordinarily noted after pneumococcal pneumonia. Only 2 patients had what might be considered relapses during late convalescence.

Epidemiology.‡ Every medical student was interviewed and careful histories of respiratory illness were obtained for the 8-week period ending August 20. This brought to light a few cases of pneumonia that might otherwise have been missed because they had not been hospitalized. In addition a survey was made of the non-student household contacts of students who lived in their own homes or with private families.§ Throughout the epidemic and for several months thereafter, all cases admitted to the hospital, both from the institutional personnel and from the outside community, were tabulated according to date of onset and date of hospitalization respectively. The first and most important fact disclosed by these investigations was that many of the cases in the student body were probably infected through contact with a laboratory instructor in Anatomy and Histology. He became ill July 18, but at that time the medical staff was not alert to the possibility of atypical pneumonia occurring in the school, and this case was missed. As he was permitted for 16 days to continue his work while

* One patient with rheumatic heart disease is excluded from this tabulation because he was advised to leave medical school for the remainder of the academic year.

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‡ Seven cases occurred among staff and students who were not admitted to the hospital and thus were not included in the description of clinical features. The history and clinical picture in these cases was such as to leave little doubt that they suffered from the same illness and they, therefore, are included in the epidemiologic report. Six cases which were hospitalized after September 30 also are included.

§ Since there are no dormitories or fraternity houses, all students live in private homes.

ill with a severe cough, all members of the first-year class were thus subjected to intimate and prolonged exposure. Under these conditions the disease seems to be highly communicable.

Chronologic Distribution of Cases. A comparison of the chronologic distribution of cases among 1238 members of the institutional personnel with that among other persons in the community is shown in Figure 1. Of the 34 cases occurring in the student body during the last 6 months of 1942, 28 had the onset of their illness during the first 3 weeks of August, and of these 28 persons, 16 were members of the first-year class. Since the incubation period of this disease is estimated to be from 10 to 25 days by most observers, it is possible that many of the students who became ill during August contracted their infection from the

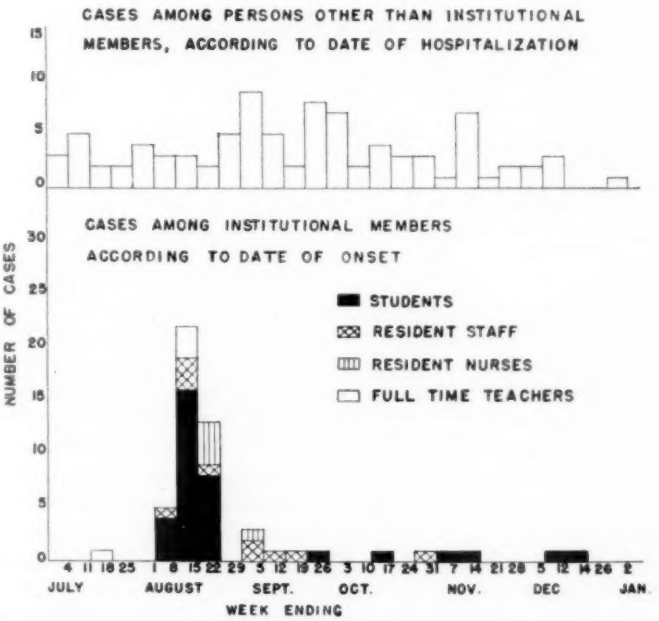

FIG. 1.—Chronologic distribution of cases of primary atypical pneumonia.

laboratory instructor whose illness began July 18. The fact that this instructor's most intimate contacts were with the first-year class lends further support to this possibility. It can also be seen from Figure 1 that relatively few cases among institutional members occurred after the month of August, although admissions from the community at large provided a rather constant source of exposure for resident and nursing staffs and upper-class students.

Distributions of Cases in Subdivisions of Institutional Personnel. In Table 7 is shown the incidence of pneumonia in various subdivisions of the hospital and medical school personnel. The absence of cases among employees and non-resident nurses may be more apparent than real since these groups are not served by the hospital medical service,

and these cases, therefore, might not be reported. If these groups are excluded from consideration, the incidence in students, resident nurses and staff and full-time teachers was 8.45%.

The outbreak rapidly assumed striking proportions chiefly in the first-year class where the total incidence was 18 cases or 26.9%. As related above, 16 of these 18 cases developed during the first 3 weeks in August (in fact, from August 7 to 18) and seem to have been caused for the most part by the laboratory instructor. Among the resident and nursing staffs and the upper-class students working with hospital patients, the incidence was much lower, as noted in Table 7, and there was a distinct tendency for cases to occur in those who cared for patients with atypical pneumonia.

TABLE 7.—INCIDENCE OF PRIMARY ATYPICAL PNEUMONIA IN VARIOUS GROUPS JULY 7, 1942–JANUARY 2, 1943

Group	Total	No. cases	% ill
First-year students	67	18	26.9
Second-year students	63	7	11.1
Third-year students	60	6	10.0
Fourth-year students	55	3	5.5
Resident staff	65	10	15.4
Resident nurses	185	5	2.7
Full-time teachers	132	4	3.0
Non-resident nurses	155	0	
Employees	456	0	
Totals	1238	53	4.27

Contagiousness of the Disease. As mentioned previously, a survey was made of the non-student household contacts of students in an effort to evaluate the communicability of cases and the possibility that other respiratory illnesses might be subclinical cases capable of transmitting the disease. The results shown in Table 8 are for 402 such contacts interviewed in the period September 6 to 9, about 3 weeks after the occurrence of the majority of cases in the student body. The respiratory infections are divided into pneumonia, simple upper respiratory infections (URI) and respiratory illnesses with constitutional symptoms (suspicious).

Of these 402 contacts none developed pneumonia, even though 46 had been living in the same house with pneumonia patients. Of the 45 contacts of students who had illnesses regarded as suggestive of atypical pneumonia, only a single suspicious case was uncovered. In the group of 200 contacts of students who had not been ill, another suspicious case was found. The only statistically significant increase in incidence of disease (15% of 111 contacts) consisted of simple upper respiratory infections in the group exposed to such infections. This suggests that under the conditions of contact described, the agent of atypical pneumonia is not highly communicable, nor is there an increased frequency of apparently related (suspicious) infections.

Means of Spread of the Disease. Dingle *et al.*[4] have suggested that inapparent cases act as a reservoir for the spread of the infection. Accordingly, an attempt was made to determine whether the chief means of spread of the agent of atypical pneumonia in this outbreak

was through clinically recognizable cases, or through subclinical cases and carriers. It is apparent that a majority, and possibly all of the cases in the first-year class, could be fairly attributed to the instructor as previously explained. It has also been stated above that among the resident and nursing staffs and upper-class students the majority of cases occurred in those who cared for patients with atypical pneumonia. However, the whole picture was overlaid and confused by the many opportunities for casual contact and by the fact that early in the outbreak cases were not recognized and isolated promptly. Although carriers and subclinical cases may occur, it can be stated that it is not necessary to postulate their existence to explain the spread of the disease in this outbreak.

TABLE 8.—DEVELOPMENT OF RESPIRATORY ILLNESS AMONG NON-STUDENT HOUSEHOLD CONTACTS OF STUDENTS WITHIN A SUBSEQUENT PERIOD OF 3 OR MORE WEEKS

Status of student member	No. contacts interviewed	Non-student household contacts of given groups of students					
		Upper resp. infec.		Suspicious		Pneumonia	
		No. cases	%	No. cases	%	No. cases	%
Not ill	200	16	8.0	1	0.5	0	
Upper resp. infec.	111	17	15.3	0	..	0	
Suspicious	45	3	6.7	1	2.2	0	
Pneumonia	46	1	2.3	0	..	0	
Totals	402	37	9.2	2	0.5	0	

Control Measures. When 18 students had become ill with atypical pneumonia by August 13, measures were instituted immediately to prevent exposure and to secure prompt detection and isolation of cases. It was decided to discontinue classes for the first- and second-year groups and all formal instruction for the third- and fourth-year students. Classes were resumed August 22. For a period of 6 weeks thereafter, each student was required to record his temperature at 8:30 A.M. and 4 P.M. and to report daily for nose and throat inspection. Opportunities for intimate exposure among members of the first-year class were reduced by doubling the number of laboratory sessions and increasing laboratory space to provide adequate separation of students.

Throughout the institution it was repeatedly urged that all illnesses be reported promptly to the medical service. Persons with respiratory illness and fever or constitutional symptoms were isolated until chest roentgenographs and their subsequent course indicated that they did not have pneumonia. In selecting members of the personnel for isolation, much greater significance was attached to sore throat and aching than to coryza, as explained previously. These measures were considered to be successful for the only cases that occurred thereafter were among those who came in close contact with hospital patients suffering from this disease.

Discussion. The observations presented in this paper make it apparent that the outbreak described was one of primary atypical pneumonia in a relatively closed group. But even though the disease was observed under optimal conditions, certain diagnostic difficulties and other clinical problems arose which deserve further comment.

Diagnostic Difficulties. On the basis of the observations described here and elsewhere[3,4,6,9–12,13,14] it is apparent that primary atypical pneumonia is a clinical entity. Worthy of emphasis, particularly in interepidemic periods, diagnosis is difficult clinically and, therefore, careful bacteriologic studies are needed so as to exclude such diseases as tuberculosis, brucellosis, tularemia, typhoid and paratyphoid fevers, sepsis, and atypical pneumococcal pneumonia. Because atypical pneumonia is very readily confused with tuberculosis clinically and roentgenographically, it is essential to search for tubercle bacilli routinely in all cases.

In recent years physicians have acknowledged the importance of routine blood cultures in cases of pneumococcal pneumonia as a guide in diagnosis, treatment and prognosis. Of equal importance perhaps is the need for routine blood cultures in all suspected cases of atypical pneumonia, for the diagnosis can never be made with any degree of certainty in the absence of a negative blood culture.

Dingle *et al.*[4] have reported negative results with sheep-cell agglutination tests in sera from patients with atypical pneumonia. However, as previously stated in this paper, 5 of 11 patients, whose admission sera were negative, developed sheep-cell agglutinins during convalescence. It is necessary, therefore, that additional sheep-cell agglutination tests, including agglutinin absorption studies, be done with serum from patients with this disease.

Another point worthy of investigation because of its unknown significance is the development of "cold" agglutinins in persons suffering from primary atypical pneumonia. Since Peterson, Ham and Finland[13] have found that "cold" agglutinins are present in the sera of the great majority of patients at or near the end of the febrile period, and since trypanosomiasis is the only other infectious disease in which these agglutinins develop regularly, it is suggested by them that their presence may serve as a diagnostic criterion.

Even if the etiologic agent of atypical pneumonia could be isolated with relative ease, virus studies are of limited value as a diagnostic measure in the ordinary hospital laboratory. The difficulties encountered in the isolation of an etiologic agent from patients with this disease are better understood in the light of the recent report by Horsfall and his co-workers[7] which indicates that at least some of the cases have been caused by a virus that is either identical with or closely related to the mongoose infectious virus isolated by Weir and Horsfall[17] in 1939.

The literature contains numerous references to the clinical and pathologic similarity of atypical pneumonia and psittacosis (also ornithosis). In an attempt to bring out some of the important differential characteristics, the outstanding clinical features of pneumococcal, atypical and influenzal pneumonias and psittacosis have been tabulated (Table 9). Perusal of this table and that presented by Goodrich and Bradford[6] indicates that atypical pneumonia and psittacosis occupy a more or less intermediate position between pneumococcal and influenzal pneumonias.

TABLE 9.—DIFFERENTIAL DIAGNOSIS OF 4 TYPES OF PNEUMONIA*

	Pneumococcal	Atypical	Psittacotic	Influenzal	
Onset	Abrupt	Insidious		Abrupt	→Same
Cough	Loose	Dry and disturbing	→Same	Loose	
Chills	1 or 2	Chilliness or repeated chills	→Same	→Same	
Pain	Pleural	Head and tracheal	→Same	Bone, muscle	
Fever	Sustained	Hectic		Sustained	Remittent
Pulse	Rapid	Relatively slow	→Same	→Same	
Respirations	Rapid	Only slightly increased	→Same	→Same	
W.B.C. count	High	Normal in early stages	→Same	Low	
Sputum	Rusty	Scanty and tenacious	→Same	Bloody	
Convalescence	Short	Prolonged with asthenia and depression	→Same	→Same	

* Many important qualifying phrases have been omitted for the sake of brevity.

Interpretation of Leukocyte Response. As previously mentioned, white blood counts ranging from 12,000 to 20,000 cells per c.mm. were recorded during or soon after the period of lysis in 11 severely ill patients. Although a similar degree of delayed leukocytosis has been noted by others,[3,6,9,11,15] this feature of the disease has never been emphasized. Its proper interpretation is obviously a matter of considerable importance because one is tempted to assume that it is an indication of secondary bacterial invasion and to institute sulfonamide therapy on the basis of this assumption. However, most observers agree that complications are rare and it has actually been suggested[9] that this disease increases host resistance to bacterial infection. On the other hand, Rhoads[14] is of the opinion that bacterial complications are more frequent and important than previously realized and that the routine use of sulfonamide is probably justified.

In only 4 of the 40 patients under consideration was there any suggestion of bacterial infection to account for the delayed leukocytosis. One had acute otitis media which cleared without myringotomy, and as previously mentioned, 3 patients had appreciable numbers of colonies of beta-hemolytic streptococci in their throat cultures. In addition, a number of patients developed laryngitis at about the time of the maximal leukocyte response, but laryngeal cultures were not taken. The few colonies of staphylococci and higher type pneumococci isolated by culturing the flora of the throat and sputum during the period of leukocytosis can probably be regarded as insignificant according to the criteria presented by Finland.[5] Moreover, it was observed that most of the patients appeared to be over the critical phase of the illness at the time when leukocytosis developed and that sulfadiazine seemed to exert no specific effect at this stage. It is our opinion that the delayed increase in the number of white blood cells does not indicate, in most instances, the presence of bacterial complications and that it, therefore, might be considered a response to the primary infection, or in other words a part of the natural course of the disease. Stephens[16] has shown that a marked stimulation of the myeloid bone marrow elements occurs during resolution of pneumococcal pneumonia and he has suggested that this might be due to liberation of nucleoproteins. Perhaps the resolution of atypical pneumonia has a similar effect upon the marrow.

As the significance of the delayed leukocytosis in this disease has not been explained by any of the studies reported to date, it is suggested that repeated cultures be taken of all possible foci of infection and that repeated Schilling differential counts and blood uric acid determinations be made in an attempt to clarify this problem.

Sulfonamide Therapy. During the outbreak described sulfadiazine was given to 16 of the 40 patients in adequate, controlled dosages, but did not appear to alter the course of their illness. Although this has been the experience of many others, there remains some difference of opinion regarding future policy with reference to sulfonamide therapy in this disease. Granted that chemotherapy is ineffective against the primary (probably virus) infection, one is still faced with two further considerations:

1. *When the patient is first seen* the diagnosis can almost never be made with certainty. For this reason there is a definite obligation to administer sulfonamide to severely ill patients while awaiting the outcome of bacteriologic studies. If these studies are not indicative of bacterial pneumonia, sepsis or other infection known to respond to chemotherapy and the patient's course and Roentgen rays point to atypical pneumonia, it is desirable to discontinue the drug promptly. This suggestion conforms with that of Janeway[8] who has emphasized that in the treatment of most acute infections it is best to give full doses of sulfonamide from the start and to discontinue them abruptly within 3 days if no response can be achieved, or if a diagnosis of sulfonamide-resistant disease (such as typhoid fever or atypical pneumonia) can be established. When one first sees a less severely ill patient with probable "atypical" pneumonia, there appears to be considerable justification for withholding chemotherapy. In this situation, as in many others, the physician must weigh the probable effectiveness of the drug on the one hand and the possible toxic reactions on the other.

2. *Later in the course of the illness* the question of sulfonamide therapy again presents itself if the patient has (*a*) delayed leukocytosis as previously discussed; (*b*) secondary rise in temperature with or without other clinical suggestion of relapse; or (*c*) frank, clinical relapse. Under any circumstances, the decision regarding chemotherapy depends upon the results of complete bacteriologic studies and upon the judgment and previous experience of the attending physician. In our experience administration of sulfonamide late in the course of the illness is seldom justified.

"Immune" Transfusions. As previously described, 12 patients were given transfusions of plasma or whole blood from convalescent donors without any definite response. A number of other observers have reported similar experience with 1 or 2 patients each. As a result of these combined observations it appears that such transfusions cannot be expected to have any specific effect on the course of the disease. If transfusions are indicated as a general supportive measure, it would seem more judicious to exempt a recent patient who is in the midst of a long convalescence and to draw the blood from a healthy donor.

Conclusions. 1. Primary atypical pneumonia is a disease difficult to diagnose on clinical and epidemiologic grounds and therefore a "missed case" may be of great importance in its spread.

2. Infection usually produces a characteristic clinical picture, but this can easily be confused with a number of other diseases. A positive diagnosis is finally established only when Roentgen ray examination of the chest reveals typical findings, bacteriologic studies are negative, and the subsequent course of the illness is consistent.

3. Under ordinary conditions of exposure, primary atypical pneumonia is not highly communicable in comparison with the common cold or influenza. If subclinical cases or healthy carriers occur they are probably of minor importance in transmission of the infection.

4. Treatment of primary atypical pneumonia is symptomatic only. Sulfonamide therapy is ineffective against the primary (probably virus) infection, but because of diagnostic difficulties, its temporary use in full doses is obligatory in seriously ill patients until bacterial pneumonia, sepsis and other infections responding to chemotherapy can be excluded. The use of sulfonamide therapy later in the disease depends upon the nature of complications, which fortunately are rare, and is influenced by the interpretation placed upon the rising leukocyte count—a feature of this disease which has often been observed but to date has been inadequately studied. Transfusions of whole blood or plasma from convalescent donors appear to have no specific effect.

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PROGRESS
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IRVING J. WOLMAN, M.D.

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GASTRIC DIGESTIVE SECRETIONS IN INFANCY AND CHILDHOOD: A REVIEW

By Irving J. Wolman, M.D.

In adult medicine, gastric analysis is falling into neglect. The great range of normal variations from day to day and from subject to subject, as well as the inconstancy of the secretory patterns in ill-health, frustrates the diagnostic application of the procedure in all diseases except a few varieties such as pernicious anemia and roentgenologically confusing stomach ulcers.[125] Pediatrics has sensed this difficulty, and of late years has directed most of its interest in digestion toward the more fruitful problems of absorption, metabolism and nutrition. The most frequent cause for aspirating children's gastric contents at present is the search for tubercle bacilli. Nevertheless, research in stomach physiology is going on persistently, and fresh studies on gastric function during childhood are constantly being reported.

No broad survey of the secretory responses of the child's stomach has been published since the somewhat limited discussion in Freudenberg's[42] classic monograph on Verdauung im Säuglingsalter, which appeared in 1929. Stewart[134] prepared a list of most of the reports on gastric acidity in health and in anemia published between 1920 and 1934. The present Review is not a comprehensive inventory of all prior articles, but rather a bird's eye summary of current beliefs and problems.

Rennin. *Nature.* Gastric juice of vertebrates, from fish upward, will coagulate cow's milk.[18a] With nearly all species the clotting is effected by the pepsin or other proteases present, for most proteoclastic enzymes can cause milk to clot.[110] However, in the case of the calf and the kid—but in no other species nor in the adult cow or mature goat—the stomach elaborates an additional powerful milk-clotting enzyme known as rennin.[51] Coagulation in these young animals is useful in impeding the otherwise quick passage of liquid milk into the intestine, in order to hold it in contact with the gastric juices for a long time.

Crude extracts of calf stomach wall rich in rennin are obtainable commercially as liquid rennet, rennet powder and rennet tablets. The dairy industry requires large quantities of liquid rennet to mix with fresh milk in the first stage of manufacture of sundry cheeses. Housewives and

dietitians employ rennet products for making milk foods and flavored sweetened rennet custard desserts. Coagulated rennet custards are useful in the feeding of sick patients and young children as well as of healthy adults, as they make milk more wholesome,[27] are more readily digested[131] and help to augment the daily intake of milk.

Action. Rennin coagulates the colloidal suspension of casein in milk irreversibly. This is regarded as the initial phase in hydrolytic dissociation of the complex protein molecule. vanDam[142a] had stated that lab (rennin) could digest calcium paracaseinate, with the most favorable hydrogen ion concentration being what is now known as pH 5. Later workers (Freudenberg,[41a] Inichoff,[73] Matthiessen,[97a] Willheim[144]) found no increase in amino acid content of various milks by formol titration before and after coagulation with labferment. Current studies,[131] however, applying the Kjeldahl technique to soluble filtrates of the whey, are revealing that rennin coagulation is followed by more advanced cleavage of the casein and other proteins, indicating breakdown of some amino acid-carboxyl linkages, though rennet extracts only have been investigated for this behavior and not pure crystalline rennin. Traces of pepsin in the rennin-containing materials tested could cause the weak proteolysis which has been observed.

The chemistry of milk clotting as induced by rennin is not well understood. The hypothesis of Linderstroem, Lang[88a,b] is the one generally accepted at the present time. According to this, casein as it occurs in its original form in fresh milk exists as a system of three components, one forming a protective colloid for the other two. Rennin attacks the protective colloid, thereby destroying the stability of the whole casein system. As shown by increased sensitivity of the casein to the effects of pH and heat, the colloidal equilibrium becomes disturbed, but precipitation does not ordinarily occur unless ions of calcium or some other earthy alkali are present. With milk itself the content of calcium is more than adequate to permit this second step in the coagulation reaction to take place, the coagulum receiving the name of calcium paracaseinate. It is not known whether coagulation reactions between pepsin, trypsin, papain and other proteolytic enzymes and milk are dependent upon the same mechanisms and the identical internal molecular rearrangements as in coagulation by rennin from the calf's stomach.

Purification. Fenger,[38] Luers and Bader,[90] Tauber and Kleiner[136a] and Hankinson and Palmer[54] have attempted to isolate rennin in highly purified form. The results obtained by these investigators with regard to the chemical and physical characteristics of the enzyme have been conflicting and highly contradictory, though all data suggest that the enzyme is either a protein in itself or performs its function in association with protein structures. All preparations displayed a manifold increase in milk-clotting potency when compared with the original gastric extracts while the peptic digestive power became diminished markedly. Thus Hankinson and Palmer's concentrate, obtained from an initial commercial rennet of high strength, showed rennin activity increased 4.55 times but with peptic activity decreased to 6.25% of that of the original extract. Very recently Hankinson[55] reported the isolation of crystalline rennin by a complicated series of "salting out" and dialyzing procedures. The crystals secured were somewhat needle-shaped and contained 1.46% sulfur, no iron, and questionable traces of phosphorus and copper. The isoelectric point was in the zone pH 4.45 to 4.65. The milk-coagulating power was very active. Peptic digestion assays were not carried out, presumably because

of the small amount of crystalline matter available for study. The results of further studies on the exact chemical nature of these crystals are awaited with interest.

It is interesting that rennin as withdrawn from the fourth stomach of the calf exists partly in the inactive precursor pro-rennin phase and partly in the activated form as a consequence of contact with the acid component of the secretion. A slightly acid reaction converts pro-rennin to rennin, the optimum circumstance for this process being pH 5.25.

Measurement of Activity. Rennin strength is measured and expressed in terms of milk-clotting power. For instance, 1 part of Luers and Bader's refined dry substance coagulated 16,440,000 parts of reconstituted milk substrate. Many variations in the technique of performance of this test have been proposed. In Tauber's[135] experience, best results are obtained when an equal volume of molar acetate buffer of pH 5 is added to the milk substrate, thus correcting for variations in pH intrinsic to different batches of cow's milk. Tauber sets up a series of test tubes containing 10 cc. of buffered milk at room temperature and varying amounts of the enzyme solution to be tested. The amount of enzyme which causes a clot in 10 minutes is taken as the measure of the potency of the specimen. However, as Hankinson and Palmer[54] point out, the relative milk coagulating activity of rennins obtained at different times by different investigators cannot be compared in exact quantitative terms. Not only do substrates vary but precise optimum conditions are usually not determined with respect to either the specimens of milk used or the relationships between Ca ions and pH, factors which affect the rapidity of coagulation and its completeness. Attempted comparisons are complicated further by the presence of contaminating pepsin, for which optimal conditions differ also.

Absence From Human Stomach. The erroneous concept is widely held among physicians and implicitly subscribed to in many textbooks that the milk-clotting action of human gastric juice is a function of contained rennin. As a matter of fact, however, that human gastric glands are able to elaborate true rennin has never been demonstrated. Gastric pepsin, and not a second ferment rennin, seems to be the agent responsible for the coagulation of ingested milk. Pepsin coagulates milk in the same manner as does rennin. Pepsin gives rise to clots and curds which cannot be distinguished by size and consistency from those produced by rennin,[131] in the pH range in which the latter is active.

The evidence which indicates that the human stomach does not secrete true rennin may be summarized as follows:

(*a*) Numerical expressions for proteolysis and coagulating strength of human gastric juice bear a reasonably constant ratio or quotient to each other.[3,68] This ratio is the same for different individuals as well as for infants, children and adults.[4] Chemical manipulations or heat, when so applied as to partially destroy or inhibit enzyme activity, interferes with both enzymatic manifestations to a parallel degree; the pepsin/rennin ratio does not alter as it should if two separate enzymes were present in the specimen, one a little more sensitive to destructive influences than the other.[68] It is possible, on the other hand, with extracts from the fourth stomach of the calf, to separate a coagulating fraction from a digestive fraction by precipitation with magnesium carbonate. This argues for the separate existence of both pepsin and rennin in the calf.[52a]

(*b*) When solutions of pepsin and rennin are mixed together in the laboratory, it is possible to alter the potency relationship existing between the coagulating and the proteolytic activities by adsorption upon colloidal

suspensions of casein.[4] With human gastric juice, dissociation cannot be effected by this maneuver.

(*c*) Pepsin will digest and destroy rennin when added to rennin in the presence of acid. Dotti and Kleiner[36] applied this principle to a study of adult human gastric juice, observing that no reductions in milk-clotting potency developed when gastric juice was acidified and incubated at 38° C. for 48 hours. They reasoned that if rennin were present in addition to pepsin the total clotting power would have diminished as a consequence of destruction of the rennin by the pepsin. This conclusion may be criticised on the ground that the coagulating power of pepsin is increased many times faster by increase in acidity than is that of rennin. Therefore it is conceivable that with a mixture of rennin and pepsin in an acid medium any tendency to decrease in clotting power due to digestion of rennin by pepsin might be counterbalanced by the increase in coagulating power of the pepsin due to the increase in the acidity.

(*d*) Differences in chemical behavior distinguish the two enzymes. The effect of rennin ceases with coagulation of milk, but pepsin continues the hydrolysis far beyond the paracasein stage. Rennin can withstand exposure to pH 9 for a short time whereas weakly alkaline solutions inactivate pepsin very quickly. Contrariwise, strong acids will inactivate rennin but not pepsin. The hydrogen ion concentrations for optimum activity are widely separated, that for rennin being pH 5.35,[92] for pepsin about pH 1.8.[107a]

(*e*) The preliminary studies of Hankinson[55] on his new crystals indicate, if substantiated, that purified rennin possesses quite a different molecular structure from that of Northrop's[107f] crystal pepsin.

Pepsin. *Crystalline Pepsin and Its Properties.* Schwann as early as 1836 had found and named the proteolytic factor in gastric juice, but it was not until nearly a century later, in 1930, that Northrop[107b,d,e] isolated animal pepsin in crystalline form. Crude extracts of secretory mucosa contain not only true pepsin but also other proteinases among which Brücke pepsin, gelatinase and cathepsin have been isolated and identified (*vide infra*). Hexahedral crystals of pepsin in apparently pure form can be prepared from extracts of swine and of bovine mucosa. Crystalline pepsin has a high content of tyrosine, dicarboxylic acids and tryptophane, and is destroyed rapidly by dilute alkali. The isoelectric point as measured by cataphoresis lies close to pH 2.7, but in solution this value is even more acid than pH 1. The optimum pH for the proteolytic activity of pepsin is about 1.8 when casein is the substrate; about 2.2 when gelatin or hemoglobin is used.[107a] The molecular weight lies between 25,000 and 40,000. Peptic activity decreases rapidly as the pH number rises from 2 to 7, becoming very weak at pH 4 and completely inhibited by pH 7.[52,60] Neither in morphology nor in rates of digestion of different substrates nor by precipitin tests are the crystals from swine distinguishable from those from bovine juice. The solubilities however are independent and different as are their responses to specific inhibitory substances, suggesting that pepsins vary slightly in structure from species to species as do the hemoglobins. Human pepsin has not been isolated in the crystalline state.

Fruton and Bergmann,[44,45] studying hydrolysis of synthetic peptides by different pepsins, found that the splitting occurs exclusively at the peptide linkages which involve the amino group of the aromatic amino acids. They noted many deviations from the generally accepted optimum of pH 2 for pepsin action on proteins, and concluded that this observed optimum represents the average of the optima for the various peptide linkages

attacked by pepsin. Very recent studies[2,132,138] indicate that Northrop's crystalline preparations are intrinsically a mixture of several component forms of pepsin possessing differing chemical properties.

Physiology of Secretion. Ever since Heidenhain's time, histologists have concluded that the proteinase or pepsin of gastric juice is elaborated by the zymogenic body chief cells of the fundus mucosa.[69,70,87,98] The content of zymogen or pepsinogen granules in the cells is highest when fasting, lowest just after a meal. Proteins are good stimulants of pepsin secretion in dogs, with formation proceeding at a constant rate for some hours. Experimental stimulation of the dog's vagus nerve, which produces a great increase in the pepsin content of the secretion,[17] results also in an extreme discharge of zymogen granules. By contrast, injections of large doses of histamine into dogs with Pavlov pouches or gastric fistulas fail to excite the production of pepsin even though marked increase in acidity becomes evident. In man, interestingly, under the usual conditions of histamine stimulation an increased output of both acid and pepsin[12,59,99,115,116b] may be elicited though the correlation between these two factors is not significant.[116c] Bowie and Vineberg[17] have suggested that this discrepancy between the species is apparent rather than actual or of basic physiologic importance. The flow of stimulated juice may do no more than flush out secretory products already present within ducts and cells.[72] Thus there is no unequivocal proof that humoral stimulation in human beings plays an important rôle in the rate of pepsin production.

Langley[83] in 1882 had noted that a slightly alkaline extract of fresh gastric mucosa contained an inactive substance which was not changed by alkali as is pepsin but which became transformed into pepsin when the solution was acidified. This precursor, *pro-pepsin* or *pepsinogen*, was crystallized finally by Herriott[61] in 1938, who isolated needle-shaped crystals of protein nature which on later acidification and recrystallization yielded another form of crystal identical with Northrop's commercial pepsin. Conversion of pepsinogen to pepsin within the stomach takes place as a spontaneous autocatalytic reaction, accelerated by pepsin itself. Immunologic studies[126] of crystalline pepsin and pepsinogen show them to be immunologically distinct from each other and their homologues of other species, though some cross-reactions do take place.

Northrop's studies have shown that the relative rates with which crystalline pepsin hydrolyzes various proteins in acid media do not differ significantly from the rates exhibited by crude gastric juice. This is taken to mean that the essential proteolytic factor in gastric juice is pepsin. The observations of Freudenberg and Buchs[43] on cathepsin indicate that proteolysis within the human stomach is somewhat more complex.

Measurement of Activity. When a protein solution is acted upon by an enzyme mixture a number of separately distinguishable chemical and physical changes can result. Hence when determining the enzyme potency of an impure preparation, if whether the catalyst present is single or multiple is not known, it is good if feasible to investigate more than one single property of the protein or to measure the activity by means of two or more substrates. In the case of human gastric juice, since the active protease has been believed to consist almost exclusively of pepsin alone, popular usage has considered as adequate for assay of potency any one of the changes this enzyme produces upon a single substrate.

In actual clinical practice dozens of techniques have been employed for the quantitative measurement of peptic strength of gastric juice. The classical Van Slyke[140] amino titration utilizes the special property of nitrous acid to attack free amino groups, liberating nitrogen which can be

caught and measured. Sörensen's[130] formol titration rests upon the tendency of formaldehyde to destroy the alkaline effect of free amino radicles. When a protein disintegrates in the presence of formaldehyde, free carboxyl groups which accumulate can be titrated against standard alkali. Measurement of the milk-clotting strength can be secured with a modified viscosimeter[82] or by direct observation of the specimens.[8,58] This principle is in wide use. Northrop[107c] determined the changes in viscosity of gelatin, casein and edestin colloidal solutions when exposed to pepsin and also ascertained the increase in formation of soluble nitrogen by the micro Kjeldahl apparatus. Manchester[94] took narrow strips of protein made from sheep gut sausage casings or of cooked egg albumen, suspended in pepsin-containing test solutions. A small metal clip was attached to the free end of each strip; the time of breaking was taken as the index of enzyme strength. Bloomfield and Polland[116b] measured disintegration of edestin by gastric juice. Anson and Mirsky[6a,b] developed an excellent though difficult technique for estimation of proteinases, using hemoglobin. Pepsin will attach hemoglobin; the extent of hemoglobin digestion can then be determined by precipitation of the undigested material with trichloracetic acid, and measuring the concentration of soluble amino acids in the filtrate which give a blue color with phenol reagent.[39] This method has been simplified by Beazell *et al.*[9] for the less sensitive purposes of the physician's laboratory. Gilman and Cowgill[46] proposed the photometric determination of the amount of silver liberated by the digestion of an exposed and developed photographic film; Osterberg, Vanzant and Alvarez[109] found this method very satisfactory. Mett's capillary tubes filled with coagulated egg albumen[100] have been given up by many workers[1] because of uncontrollable inaccuracies inherent in the procedure. There seems to be no need to go further in enumerating the available procedures for estimation of pepsin in gastric juice, especially since such examinations have not proved of much value clinically.

Since there is no rennin in human gastric juice and since coagulating of milk represents the initial stage in the proteolytic digestin of casein by pepsin, the concentration of pepsin may be ascertained by measuring the time required for any given solution to clot milk. The results are compared with control values secured by use of standard pepsin in known dilutions.[8,16d,58,60] For the average physician's office or clinical laboratory lacking special facilities and equipment such simple, rapid methods based upon milk-clotting power are reasonably accurate and easy to work with.

Clinical Observations. Osterberg, Vanzant and Alvarez[109] described the difficulties involved in utilizing pepsin measurement as a clinical tool. Fasting specimens were observed to vary widely, the fasting findings in 24 normal males ranging from 5 to 1930 units (Gilman and Cowgill technique). This extreme variability was ascribed in part to contaminating secretions from saliva and duodenum. More consistent results were obtained following a Ewald type meal, the values ranging from 0 to 580 units. Repeated tests on the same individuals on successive days showed great lack of uniformity. The figures for males averaged higher than for females. These authors concluded that no reading could be termed abnormal unless it lay well beyond the range of normal values.

Studies on adults (8113) have shown that pepsin is frequently recoverable from patients with complete anacidity. Evidently the secretion of gastric enzymes may persist after acid secretion has stopped. In cases of pernicious anemia, cancer of the stomach and severe gastritis, the pepsin output is diminished, often to extremely small amounts.

The presence of a ferment capable of coagulating milk and attacking

egg white in the gastric juice of unfed infants but a few hours old has been detected by many workers.[62,85,117,134,152] That this enzyme exists in the gastric secretion of infants and children is plainly evident by the curds present in regurgitated milk meals. Ogilvie,[108] one of the latest workers to study gastric pepsin, determined its content in health, anemia, rheumatic fever, and celiac disease, using the Mett tube method. The figures obtained showed wide variations, but no instance of deficient pepsin was encountered. Steimann[133] encountered 1 case of absent pepsin in 100 children examined. Jacobsen,[74] Chievitz[23] and Muhl[105] have reported instances of full achylia with both pepsin and free acid absent. Subsequent examinations on these cases were not performed.

For a summary of older observations on pepsin in health and disease, Freudenberg's monograph[42] may be consulted. The Reviewer has failed to uncover any large series of pepsin determinations on normal growing children, performed by modern reliable methods, to indicate that a differential rate of secretion as related to age takes place with pepsin, similar to that for hydrochloric acid.

All investigators who have studied gastric function in infants with test meals of milk have noted that cow's milk mixtures rarely attain a hydrogen ion concentration lower than pH 4, even after remaining in the stomach for 2 hours or longer. Breast milk, in contrast, because of its lower buffer capacity in conjunction with the abundant formation of fatty acids from the action of its own lipase, may attain a pH of 3 or lower. Since, as has been noted, pepsin does not exert any appreciable proteolysis on casein until the pH has dropped below 4, and has maximal action at 1.8, the conclusion seems inescapable that during infancy pepsin contributes little to the breakdown of milk proteins, apart from causing coagulation to take place. With older children[148] in whom the secretion of acid is more abundant, the pH of ingested milk will ultimately fall below 4, sometimes as low as 2, but only after a significant interval of time has gone by.

Cathepsin. *Properties.* In 1940 Freudenberg and Buchs[20,41b,43] announced that the proteolytic enzyme cathepsin, which had been discovered in the intrinsic tissue of the stomach wall by Willstätter and Bamann[146] in 1929, was present in quantity within the gastric secretion. Cathepsin is an intracellular enzyme recoverable from nearly every body tissue, though most abundant in leukocytes, lymphoid organs, kidneys and liver. It acts best at pH 4 to 5,[41c] and is inert at neutrality. Hence, within living cells this substance is probably inactive. After death, however, as the intracellular hydrogen ion concentration rises through anaërobic production of carbonic, lactic and other acids, the proteolytic effect upon the tissue proteins becomes manifest as a major element in autolysis.[18b] Willstätter had believed that the cathepsin recoverable from the stomach lumen originated in leukocytes migrating from the lymph follicles of the mucosa. Freudenberg and Buchs on the other hand maintain that cathepsin is a true secretion, pointing out that the rapid rate of its formation and failure to reduce the concentration in fresh juice by centrifuging off the leukocytes permit of no other interpretation.

Significance in Gastric Juice. For years the workers in the field of infant feeding had been suspicious of the presence of a second proteolytic enzyme in gastric juice, operative at the isoelectric zone of the milk proteins. Rosenbaum and Spiegel,[121a] Mathiesen,[97a] R. Hess,[63b] and Budde[21] had all incubated gastric juice with milk under conditions of low hydrogen ion concentration and observed a subsequent increase in soluble nitrogen formation. This increase could not be explained in terms of pepsin action, since with *in vivo* studies pepsin proves active only with strong acidities

(pH 1 to 3). That cathepsin might explain this puzzling phenomenon had been mentioned by Freudenberg as early as 1929,[42] but not until a decade later did he succeed in demonstrating its actual presence in quantity in the gastric juice.

Freudenberg and Buchs[43] studied the proteolytic power of many specimens of gastric contents, comparing digestive strength at pH 2 (optimum for pepsin) with that at pH 4.7 (optimum for cathepsin). With milk as a substrate, and increase in residual nitrogen in mg. per 100 cc. as the index of activity, these data were obtained:

	Pepsin	Cathepsin
54 infants	46.5±3.26	27.4±2.07
16 older children	99.2±8.90	78.1±6.67

Similar data were secured with a half dozen adults. With several infants the cathepsin figures exceeded those of pepsin. In general cathepsin potency seemed to range between 50 and 100% of that of pepsin. It was noted that more marked digestion seemed to take place with juice from infants being raised on cow milk mixtures than from breast-fed infants.

Differentiation From Pepsin. Cathepsin was found to be most active at 63° C., a temperature at which pepsin and most biologic ferments are partially destroyed. At this temperature (63° C.) its digestive potency exceeded that of pepsin at 45° C., which is optimal for the latter. Hydrogen sulfide augmented cathepsin activity a little. Following the mixing of gastric juice with a number of different chemicals the toxic effects upon the cathepsin and pepsin components were in some instances parallel, in others divergent. Cathepsin attacked casein, lactalbumin and egg albumen—true proteins—but had no influence on the several dipeptides tested. Early attempts to separate the gastric juice into two fractions, each containing one of the proteolytic enzymes, were not wholly satisfactory. Best results were secured by adsorption upon cholesterol. Very recently, however, Freudenberg[41c] did succeed, by selective precipitation procedures, in obtaining a pepsin-free solution of gastric cathepsin. The milk coagulating or rennin-like titer of gastric juice specimens was in no way proportional to cathepsin content. Cathepsin-containing extracts when activated at 37° C. by hydrogen sulfide showed no parallel increase in clotting strength. Indeed, following warming to 60° C., the clotting power became markedly weakened in spite of the fact that the activity of the proteolytic factor was enhanced by the procedure. Purified cathepsin-containing preparations exhibited almost no clotting power. From these findings the authors concluded that curdling of milk in the infant stomach is not accomplished by the cathepsin present. It was their further belief, based on earlier determinations of gastric acidity during digestion, that much of the proteolysis which does take place in the infant's stomach is effected by cathepsin and not by pepsin.

These observations of Freudenberg and Buchs are new and of fundamental importance if substantiated. One can expect a wave of new investigations exploring possible application of the cathepsin factor to the many diverse problems of gastro-enterology, especially in the pathogenesis of gastric ulcer.

Minor Proteinases. *Gelatinase.* Mention should be made in passing to the recovery by Northrop[107c] of a gelatinase or gelatin-liquefying enzyme from crude preparations of bovine pepsin. This when isolated as an amorphous powder proved to be about 400 times as active as crystalline pepsin in the liquefaction of gelatin. In contrast its activity as measured by the digestion of casein, edestin or egg albumen was much less than that of crystalline pepsin. The presence of such a specific enzyme in

human juice, separate from the pepsin contained therein, has never been explored, probably because sufficiently large quantities of human secretions to yield weighable solid precipitates for the chemist to work with are well-nigh impossible to obtain.

Brücke-pepsin. Kraut and Tria[80] described the recovery from commercial pepsin, by an old method used by Brücke, of a protein-free preparation of non-crystallizable pepsin in addition to Northrop's crystalline form of the enzyme. It has been pointed out[107] that gelatinase and Brücke-pepsin together represent a relatively negligible part of the total proteolytic activity of crude gastric juice.

Amylase-accelerating Factor. Davison[32b] has called attention to the amylase-accelerating action of gastric contents. The addition of infant gastric contents to fresh hog pancreas extracted in saline solution increased its starch-liquefying activity nearly eight-fold.

Lipase. *Properties.* Not many facts are known about the gastric lipase. Its presence explains the distinctive odor of butyric acid recognizable when vomiting follows milk or any meal containing butter fat. There is some uncertainty as to whether in humans it is secreted directly or enters the stomach by the route of duodenal regurgitation, but Freudenberg[42] and others[10,31,86] who have studied the subject consider that the gastric wall can and does produce a lipolytic enzyme of weak potency. The optimum hydrogen ion concentration for its activity is pH 4–5. Unfed newborns have gastric lipase,[62] and it appears to be constantly present through infancy and childhood.[49a]

Breast Milk Lipase. Freudenberg[42] carried out extensive studies on fat digestion with special attention to breast milk fat. It appears that both breast milk and cow's milk contain a certain amount of natural lipase, which is thermolabile. In the case of cow's milk this enzyme becomes destroyed during pasteurization or boiling. With breast milk, on the other hand, which ordinarily receives no heat treatment in advance of being fed, the contained lipase appears to play an important rôle in the digestive breakdown of fats, acting through several interesting mechanisms. For one thing, the optimal hydrogen ion concentration for breast milk lipase lies between pH 7 and 8; at pH 6 its performance is reduced to one-half; at pH 5 to one-tenth. Regurgitation studies show that with young infants receiving breast milk, which is normally slightly alkaline, the acidity of the gastric contents following nursing does not fall to pH 6 until 30 minutes, and pH 5.5 is not attained until nearly 2 hours. Thus conditions for lipolysis remain favorable long enough for an appreciable fraction of the butter fat to break down. With older infants the more liberal secretion of hydrochloric acid and the fatty acid formation act together to produce conditions of high acidity in the stomach.

Lipokinase. Breast milk when left standing at room temperature for some hours does not grow rancid, yet when mixed with gastric juice becomes rancid immediately. Freudenberg[42] extracted a thermolabile glycerin-soluble lipase-activating agent from the gastric wall of some species of animals and demonstrated the presence of this same agent in human gastric juice both during infancy and throughout life. This he named "lipokinase." The function of the lipokinase is to activate the fat-splitting enzyme which in fresh breast milk occurs in an inactive or "pro-lipase" state.

Hydrochloric Acid. *Physiology of Secretion.* All current work points to the parietal cells as the source of gastric acid.[30c,48,65c] The histologic evidence[33,64] suggests that these cells secrete an unidentified alkaline or weakly acid chloride compound which hydrolyzes to yield hydrochloric acid as the

secretion wells out of the gastric foveolæ. Biochemical studies, however, indicate that the parietal secretion is formed directly as an isotonic solution of pure hydrochloric acid, with perhaps a little potassium chloride mixed in. One must marvel at the ability of these single cells to alter the concentration of hydrogen ions more than a million times. The negative Cl^- ions which accompany the H^+ ions come from the neutral chlorides of the blood and lymph. This is shown by the lower concentration of chloride ions in the venous output from the stomach when secreting, as compared with the arterial supply tested simultaneously. The reactions which liberate the positive hydrogen ion are very obscure. Many hypotheses have been proposed.[21,53,65c,97] Surface membrane phenomena undoubtedly play an important part. Davenport[30] has suggested that the production of carbonic acid from carbon dioxide and water under the influence of carbonic anhydrase is a necessary intermediate step. Equally obscure is the mystery of the regulation of intensity of acidity within the gastric contents. Rosemann,[121] Katsch *et al.*,[75] and other workers[93] had contended that the extent to which the stomach converts plasma chlorides to hydrochloric acid depends upon the intensity of the secretory stimulation. However, the theory more widely held, first advanced by Pavlov,[112] is that the gastric hydrochloric acid is secreted from the mucosa glands at a high and more or less constant concentration under both normal and pathologic circumstances, regardless of the *rate* of secretion. Thus Hollander[65a,b] calculated that the parietal secretion of dogs would consist essentially of free hydrochloric acid and water, in a concentration of 165 to 170 mg. per liter, and demonstrated specimens from fundic pouches which were nearly of that strength. Gray[48] confirmed Hollander's figures for chloride, but stated that the parietal secretion consists of 166 mg. per liter of Cl^- ion, 159 of H^+ ion, and 7 of K^+ ion. Teorell[137] had interpreted the changes in acid buffer solutions introduced into cat stomachs as meaning that the "primary secretion," expressed as hydrochloric acid, was a little less than 208 ± 6 mg. per liter. The figure given by Hollander as representing the approximate concentration of the original acid secretion becomes, when expressed in more familiar terms, 0.6% HCl, with a pH value of 0.87; 100 cc. will be neutralized by about 165 cc. of 0.1 N alkali (165 chemical "units" of acidity).

Acidity-reducing Mechanisms. Regardless of the precise strength of "primary" juice, all workers are agreed that secondary acidity-reducing mechanisms are constantly in action to bring down the acidity strength to the lower, less concentrated values existing within the normal stomach. A number of diverse neutralizing and diluting agents mix with the freshly secreted acid as soon as it reaches the mucosa surface, and perhaps within the orifices of the secretory ducts themselves. A multitude of investigations have been directed towards these various neutralizing mechanisms.[16,65b,72,118,143] Hollander's[65b] review classifies them as follows:

A. Variation in the volume rate of HCl poured into the stomach.
B. Extragastric factors.
1. Dilution and neutralization by saliva.
2. Dilution and neutralization by regurgitated duodenal fluid.
3. Dilution by the test-meal itself (when used).

C. Intragastric factors.
1. Possible variations in the composition of the parietal secretion itself.
2. Reabsorption of HCl, already secreted, by the gastric mucosa.
3. Dilution by the peptic secretion.
4. Dilution and neutralization by a distinct dilution secretion.
5. Dilution and neutralization effects of mucus secretion from the surface epithelium.

The control, characteristics and individual importance of these factors are far from constant, varying from person to person, and even in the same individual from moment to moment. Thus, the stomach when fasting or after simple stimulation contains a composite mixture of fluids. The strength or concentration of hydrochloric acid found at any random aspiration represents the resultant of a whole series of secretory phenomena, with fluctuant components which are never constant or stable.

The bulk of the studies on gastric acid control have been carried out on experimental animals and adult human subjects. No peculiar physiologic mechanisms beyond what are known or presumed to be true for adults have been demonstrated as being operative in the pediatric age period, although the strength of acid secreted is much less in childhood than in maturity.

Purpose of Gastric Analysis. Since secretion of acid is one of the obvious major functions of the stomach, and readily determinable by simple testing, clinicians from the time of Beaumont have been measuring and recording the stomach's hydrochloric acid content in a host of normal and abnormal conditions, hoping to find in the readings a major index or criterion of the efficiency of its work. Repeated fractional examinations following simple test meals are considered by many workers to be more informative than single specimen diagnostic aspirations. Innovations and minor changes have been and are still being introduced.

Hollander and Penner[67] have reviewed the whole field of gastric analysis from the viewpoints of history, development and usefulness. Their criticisms of acidity determinations are representative in general, though perhaps not in every detail, with the experienced judgment of modern gastro-enterology, and merit the following brief summary: Single specimens of acid containing gastric juice withdrawn after any of the test meals rarely yield pathognomonic diagnostic information. Nor does the fractional method adequately fulfill the hoped-for purpose of demonstrating pathologic variations in the ability of diseased mucosa to respond to a standard stimulus. So-called "normal" curves can occur in the presence of obvious stomach disease, whereas "abnormal" curves are not uncommon among healthy individuals. Wide day-to-day variations may occur in the fractional curves obtained with any one individual with or without gastric disease. For these reasons, in addition to others concerned with details in performance of the acidity tests themselves, many physicians and institutions "have accorded to gastric analysis a forthright negation of all but a modicum of diagnostic significance." There is great need to develop and standardize all the physiologic procedures which show promise of value, and to apply the principle of fractional analysis to the study of the many individual physiologic components of gastric behavior.

Titration of Acidity. Töpfer's quantitative procedure is the technique most widely used for measurement of gastric hydrochloric acid. Ten cc. of filtered gastric juice is mixed with 3 or 4 drops of dimethylaminoazobenzol (0.5% alcoholic solution) and 3 or 4 drops of phenolphthalein (1% alcoholic solution) in a porcelain dish. N/10 NaOH is then added drop by drop from a burette until the last trace of red color disappears. This reading is noted. Titration is then continued further until the red tint of phenolphthalein has reached a maximum. The number of cc. of NaOH solution calculated to produce the first color change in 100 cc. of gastric juice is taken as the measure of free acidity. That figure was often expressed as clinical "units" and frequently written with the degree sign (°). This old system of representing gastric acidity values is being replaced rapidly by the standard notation of modern chemistry. Readings are given in normal or millinormal terms, abbreviated as N or mN respectively. Fortunately, the

numerical representation is the same, whether the unit of acidity be "degrees" or mN. The number of cc. of NaOH which would produce the second color change in 100 cc. of gastric juice similarly represents total acidity. In the present Review, for reasons of brevity, the figures will be used alone without any descriptive designation. The term "free acid" refers to the hydrogen ions not linked to the buffer substances. The "total acid" is a measure of the free acid plus the entire buffer capacity to the end-point of phenolphthalein.

Several criticisms of Töpfer's method are pertinent. Gastric juice is a buffered mixture of assorted gastro-intestinal secretions. As Michaelis first pointed out,[102] titration to the full yellow color of dimethylamino-azobenzol corresponds to a pH value of 4 to 5. It gives therefore a misleading end-point for free HCl, which falls at pH 2.8. In the pH range 3 to 3.8 neutralization of the acid proteins and the phosphates of the secretion account for much of the "combined acidity" once attributed to bound HCl.[96] Moreover the red color of phenophthalein marks a pH of 8 to 10, a reaction much more alkaline than that of the blood serum from which the acid digestive juice was derived. The indicator thymol blue would be preferable since it possesses a considerable higher degree of chemical and physiologic accuracy for free and total acidity.[127] Unfortunately the conventional method of scoring in gastric analysis carries such a weight of tradition and already accumulated data that most contemporary workers, such as Cutter,[28] are impelled to continue with it, though fully cognizant of the defects.

Total Chlorides. The total chlorides of gastric contents consist not only of secreted hydrochloric acid and its salts, but also of neutral chloride derived from the alkaline secretions of fundus and antrum, from saliva, and from regurgitated duodenal fluid. It might be anticipated that study of the balance between free and total chloride would throw light on the relative importance of the various factors in secretion, but attempts to relate changes in chloride concentration with disturbances in secretion have not proved successful. Data on total chlorides can be found in many reports[35,37,108] and have been especially investigated in children by Copeman and Hill.[26]

The Resting Secretion. Fasting secretions, collected after no food or drink has been taken for 8 to 12 hours, show extreme variability in content of all elements.[148] Single specimens are wholly unreliable as indicators of the state of secretory function.

Test Meals. MILK. A variety of foodstuffs and other substances have been proposed as standard test stimuli of gastric secretion. With infants, and with older children as well, the customary milk feeding mixture or some other related meal which the child has been taking regularly would seem the reasonable stimulus to use, for then one would get a true picture of what goes on inside the stomach during the every-day pattern of digestion. Indeed, ordinary milk meals were given for this purpose by the early students of childhood digestion, whose roster included the names of Kronenberg,[81] R. Hess,[63a] Hahn,[50] Davidsohn,[31a] Babbott *et al.*,[6] Davison,[32a] Marriott and Davison,[95] Yllpö,[151] Wills and Paterson,[145] Griswold and Shohl,[49] Parsons,[111] Demuth,[34] Klumpp and Bowie,[77] Klumpp and Neal,[78] Banu, Negresco and Heresco,[7] and Gianni.[49a]

Milk is not the best standard test meal because its buffer strength fluctuates with season of the year, breed of the cow, extent of dilution and precipitation in the formula, and size of the curds which form in the stomach.

The buffer value of cow's milk, plain or modified, is so great that the

acid free in the stomach at the moment of drinking becomes obliterated, absorbed by the buffer. For the first few minutes following ingestion, therefore, the pH of the gastric contents are essentially the same as the pH of the milk itself.[148] The pH then begins to fall slowly as the digestive secretions start pouring out. Coagulation of the milk soon takes place, complicating the chemical picture. Boluses of milk are intermittently spilling out into the duodenum at inconstant and unknown rates, further clouding the interpretation of the findings. As the consequence of the interaction of all these complex factors the slope of the pH curve given by successive samples of a milk meal withdrawn at regular intervals represents the resultant of a multiple series of changes rather than a pure secretory response.

Many valuable data helpful to an understanding of the function of the stomach as a digestive organ have been yielded by the withdrawal of milk meals subsequent to feeding. However, to analyze the rôle played by the stomach as a unit in the child's digestive system lies outside the scope of this Review, which is being confined to a study of the secretions themselves. Yet, by way of illustration, one table of data, that of Marriott and Davison,[95] is given here to show the sort of information that may be secured. Specimens were withdrawn 2 hours after feeding. The figures represent the pH of gastric contents of normal infants compared with others suffering from infectious or nutritional disturbances.

	Breast milk	Cow's milk	Lactic acid milk
Normal	3.75	5.10	3.71
Abnormal	4.74	5.35	4.10

When fever is present, acid secretion fails (*vide infra*). This agency may account for the above differences.

Barley Gruel was preferred for testing of sick and well infants by both Meyer[101] and Chievitz,[23] who reported as follows: infants secrete less acid than older children; wide variations occur within each age group and with individual children; infants being raised on milk-free or milk-poor diets secrete as much acid as those receiving abundant milk; infants with acute parenteral infections may have decreased acidity for some weeks thereafter; in chronic gastro-intestinal disorders free acid may be low or absent. Chievitz found not one single instance of achylia in 53 infants examined.

With older children the Ewald Type of Test Meal, consisting of roll, toast, shredded wheat, arrowroot cookies or cooked cereal with water or unsweetened tea, was used to obtain the data on normals presented by Hurwitz,[71] Sauer *et al.*,[124] Klementeson,[76] Copeman and Hill,[26] Wright *et al.*,[150] Wright,[149] Dietrich and Shelby,[35] and Vanzant *et al.*[142] The Ewald test breakfast is taken on an empty stomach after an overnight fast, and the contents removed by aspiration 1 hour after the start of the meal. The data in Table 1 were secured by this method.

The Alcohol Meal, consisting of 50 cc. of 7% grain alcohol injected through a small tube, has received attention because the returned material is watery and easily removed (Ogilvie,[108] Stewart[134]). Steimann[133] considered a 0.05% caffein solution equally effective. With either the Ewald or the alcohol meal "fractional" removal of gastric contents can be practised, specimens being withdrawn for testing every 10 or 15 minutes and the acidity changes followed until they return to the original fasting level.

Dietrich and Shelby[35] compared the shredded wheat and alcohol test meals in a small group of 14 children, using histamine also. It was noted that the Ewald test meal substances plugged the stomach tubes and hampered the laboratory titrations, besides being contaminated with saliva. The alcoholic solution was free from these handicaps, but was thought to represent an unusual unfamiliar stimulus to a child. Histamine produced satisfactory specimens and was of great aid in distinguishing between true and false achlorhydria. Their average values were: (*a*) 1 hour after Ewald meal, free acid 22.2, total acid 43.2; (*b*) 30 minutes after alcohol meal, free 50.3, total 71; (*c*) 30 minutes after histamine, free 89, total 114.1. Alcohol is a stronger stimulant than a carbohydrate meal, and histamine is much more powerful than either. The authors concluded that the figures for free hydrochloric acid and total acidity for healthy children present such wide variations that a normal figure cannot be stated.

The absence of any unanimity among the experts as to which type of test meal stimulus can be considered most suitable as a test for gastric functioning efficiency suggests that none of the meals fulfills the desired purpose adequately. For a more complete discussion of relative merits and faults, and details as to administration, the reader is referred to standard texts (*e. g.*, Ref. 139), and to the critical review of Hollander and Penner.[67]

Stimulation With Histamine. Response. The stomach reacts to a parenteral injection of histamine with an extreme secretion of acid. The maximum volume, maximum free acidity, maximum total acidity, and, least reliably, lowest pH number may all be measured as significant indicators of secretory strength. These factors all pass their height and subside before an hour, usually attaining highest values at about 30 minutes. Bloomfield and Polland[13] claim that repeated examinations in the same adult subject following any given dose of histamine will yield secretion curves closely resembling each other. Most workers with children have assumed that this generalization, which is based upon adult material, holds equally well with youthful subjects. Cutter[28] found that with cooperative children repeated testing over several days produced moderate variations in the fractional curves, but when a state of anger or terror persisted through the test the results were erratic and as a rule in the direction of decrease in acidity. This failure of the powerful stimulant histamine to overcome the inhibitory influence of the psychic state upon gastric acid secretion is a telling illustration of the extensive control which emotions mediate on digestion.

Dosage. With children, as with adults,[47] the response to histamine has been found to be dependent upon the size of the dose.[28,35,106,128] A small dose will evoke a small quantity of less concentrated juice. For clinical testing of stomach function the consensus has been to employ a dosage large enough to produce hyperemia of the skin and slight acceleration of the pulse rate, without more toxic symptoms of headache or collapse. The careful studies of Dietrich and Shelby,[35] Siemsen[128] and Cutter[28] indicate that 0.01 mg. of active histamine per 1 kg. body may be recommended as the optimal dosage for children of any age. In administering histamine this dosage should be calculated in terms of the amount of histamine base present in the preparation being given; *e. g.*, histamine dihydrochloride contains 60% histamine base whereas ergamine acid phosphate consists of but 36% of active substance. When performing the test it is customary to remove the gastric contents fractionally

every 10 or 15 minutes for $\frac{3}{4}$ to 1 hour while the gastric catheter rests in place. In actual performance, specimens which by a yellow color suggest contamination with regurgitated duodenal juice are discarded. The marked increase in gastric acidity which follows histamine shows that no large amount of alkaline saliva[32a] is being swallowed during the test.

NORMAL VALUES. It is not feasible or necessary to reproduce all minutiæ of the accumulated data on the results of the histamine test with children.[25,28,37,56,76,106,128] The reported observations indicate that for children, as with adults, an extremely wide range of variation can be found among individuals of the same age and state of health. The volume of stimulated gastric secretion increases in proportion to body growth as expressed by weight. The mean concentrations of acid do not increase in any such parallel proportion. Strong values for hydrogen ion concentration are attained soon after 1 year of age.

The wide scatter of the data, the limited number of observations, and the dissimilarities in technique and presentation used by the different authors make it difficult to compile an elaborate statistical presentation of normal values for histamine-stimulated juice. The following table is compiled from the sources cited. It shows the range of spread reported for healthy American children. Approximately 0.01 mg. histamine base per kilo was given. The data for secretory volume have been recalculated in terms of cc. per minute in order to get a common denominator for comparison.

Age	Secretory volume (per minute) (cc.)	Free acidity	Total acidity	pH
Prematures	0.12–0.15	0	0– 8	4.7
Newborns	0.20–0.45	0– 20	15– 40	2.3–3.6
2 wks. to 6 mos.	0.25–1.10	0– 59	5– 71	1.5–3.4
7th to 12 mo.	0.40–1.50	12– 80	25–105	1.5–2.2
1 to 2 yrs.	0.70–1.80	15– 95	26–106	1.2–2.0
2 to 5 yrs.	0.50–2.20	29– 90	38–102	1.4–2.0
5 to 10 yrs.	0.10–3.30	53–113	61–145	1.4–2.0
10 to 15 yrs.	2.70–3.60	49–115	61–128	1.4–2.0

As a comparison, the range in total acidity for normal adults as observed by Bloomfield and Polland[116d] had extended from 30 to 159 after histamine stimulation. Three-fourths of the values were over 100 and the greatest number of cases were encountered at about the 135 range.

SIGNIFICANCE IN ANACIDITY. In Dietrich and Shelby's[35] comparison of healthy children one interesting 6 year old child gave weak juice with the Ewald and alcohol test meals, the highest readings being 13 for free HCl and 32 for total acid obtained with the Ewald meal. Later, after 0.25 mg. of histamine (0.01 mg. [kilo] body weight) a rise to 105 free HCl and 145 total acid was secured. This case illustrates the universal experience that histamine stimulation should be employed with every patient who shows low secretion of acid with a test meal. A diagnosis of achlorhydria must not be made until this form of stimulation has been tried. In fact, in adult gastro-enterology, the principal use of the histamine test at present is to differentiate between false and genuine achlorhydria.[14,15]

Histamine attracts attention because it stimulates and permits measurement of pure secretions instead of the mixture of juice, food, saliva and perhaps regurgitated intestinal juices which occupies the stomach following a test meal. Unfortunately, histamine, which is injected instead of administered by mouth, gives rise to an excessive secretagogue effect in place of the more normal mucosal response which follows the natural

taking of food. From the evidence one must conclude that for children as with adults the acidity values obtained with histamine have no clinical significance apart from uncovering true instances of achlorhydria.

Normal Values Following Ewald-type Meal. For adults the well-known Mayo Clinic[141] standards for normal men, based upon a test meal of arrowroot cookies and water, group themselves about a modal range of 45 to 50 for free acid, and 63 to 66 for total acid with most workers. Histamine stimulation gives figures 10 to 30% higher, on the average, than with the Ewald meal; the free hydrochloric acid occasionally rises to 150 or even more.

TABLE 1.—VALUES FOR FREE ACID IN NORMAL CHILDREN FOLLOWING EWALD-TYPE MEAL

(Collected by Vanzant, Alvarez, Berkson and Eusterman[142])

Age (yrs.)	Males		Females	
	Mean	Standard deviation	Mean	Standard deviation
2	12.0*	8.0	9.0*	8.8
3	17.0	8.5	13.0	9.2
4	20.5	9.0	16.0	9.6
5	23.0	9.6	18.5	10.0
6	24.5	10.2	20.5	10.5
7	26.0	10.8	21.8	11.0
8	26.5	11.3	23.0	11.4
9	27.0	11.7	23.5	11.8
10	27.5	12.0	24.0	12.2
11	27.5	12.5	24.3	12.5
12	28.0	13.0	24.5	12.9
13	30.0	13.5	24.8	13.4
14	33.0	14.0	25.0	13.7
15	37.0	14.5	26.0	14.0

* Expressed as cc. N/10 HCl per 100 cc. gastric contents, or millinormal strength.

A good picture of the range of free acid in normal children after a simple Ewald-type test meal is given in the paper of Vanzant, Alvarez, Berkson and Eusterman.[142] Their figures were obtained by pooling the data of Jacobsen,[74] Klementsson,[76] Muhl,[105] and Wright[149] together with material from their department at the Mayo Clinic (Table 1). Increase with growth is clearly shown, as is also the tendency for boys to possess somewhat higher values than girls of the same age—a sex distinction which persists throughout life. One notes that the rate of rise is greater in the first few years than later on. Of striking importance is the magnitude of the standard deviation. The range represented by the standard deviation will include when added and subtracted from the mean slightly more than two-thirds of all the cases. Thus, for instance, at age 2 about two-thirds of the boys will exhibit free acid figures between 4 and 20.

It should be emphasized that this tabulation was compiled from a large group of single tests following a moderately stimulating carbohydrate meal. Other subjects of comparable age and health, or the same subjects if tested again at a later date, might have yielded statistics differing somewhat from these. In fact the data on normals from still other sources, such as Ogilvie's[108a] 60 children who had had porridge as a test meal, ran about 25% higher than the figures above given.

The figures of Vanzant *et al.* for age 1 year have been omitted from the reproduced table. There is a question how the test meals given to the younger infants in the first few months—whatever they may have been—compare in stimulant effect with the Ewald type used with the youngster beyond infancy. Again, as reference to the original sources shows, not all

the infants included in the tabulation were healthy and free from disease. Furthermore, the collecting into one single group of all infants 12 months and under masks completely the progressive increase in values which is taking place during this important year of rapid growth.

Newborn Period. Unexpectedly high acid values are found in the immediate postnatal period. This was first pointed out by Alfred Hess[62] in 1913, who aspirated the gastric contents of 55 unfed newborns under 15 hours of age. The quantity of juice obtained from each ranged from 0.3 to 5 cc., though 1 infant held 10 cc. and another 12 cc. of secretion. The possibility of this fluid consisting in part of swallowed amniotic fluid seems excluded by the further observation that on repeated aspirations free acid could be secured each time, indicative of its continual secretion. In one striking case a total of 17 cc. of highly acid gastric juice (free HCl 30 to 66) was secured within a 110-minute period. Pollitzer[117] made similar observations in a series of 100 unfed newborns. Griswold and Shohl's studies[49] on the fasting secretion in 25 normal newborns showed a pH range from 1.7 to 4.4 (numerical average 2.6).

Very recently Ritter[120] reported on the resting secretion in 36 unfed newborn infants ½ to 14 hours after birth. In over 50% of the infants the free acid was higher than 20, reaching to 56 in 1 instance. Four showed no free acid. The pH ranged from 4.6 to 1.3. Attempted stimulation by milk and barley gruel provoked little response. Forty cc. of 2% Liebig's meat extract produced increase of total acid but none of free acid, presumably because of the buffer action of the contained proteins.

Cutter[28] is the only one to report on histamine stimulation of newborns. His series is too small to establish any generalizations; but 6 of 9 newborns 10 days old and younger produced free acid with histamine, the highest value being 20.

Miller[103] systematically followed the fasting acid with 50 normal infants from the 1st day of life until 1 month of age. Nearly all were breast fed. Specimens were taken 7 hours following the preceding feeding. The gastric acidity had its highest value on the 1st or 2d day of life, and then abated until the 7th day, after which it remained at a negligibly low level. Miller's data were summarized in the following table of averages:

Day	No. of cases tested	Free acid (Töpfer's reagent)	Total acid (phenolphthalein)
1	45	17.2	38.0
2	40	15.4	37.9
3	41	4.5	24.6
4	40	1.0	21.7
5	40	0.7	22.3
6	40	0.2	17.6
7	40	0.4	14.2
8	41	0.0	14.2
9	40	0.0	14.4
10	40	0.0	11.7
11–15	41	0.7	13.8
16–20	50	1.0	16.9
21–30	45	2.1	18.0

The resting volumes recovered on aspiration were 1 to 3 cc. in the initial 2 days of life whereas after the 1st week when the acidity was feeble the volume decreased to 0.5 cc. or less.

Both Miller and Ritter suggested that the high values found in the immediately postnatal period may be caused by some gastric secretagogue substance transmitted from the mother's blood stream. In criticism of

this hypothesis one may comment that none of the known hormonal secretion-stimulating substances, such as enterogastrone, exert their influence for more than a few hours following a single administration, and certainly not for a protracted period continuing as long as a week. A likelier cause for the phenomenon may lie in the erythrocyte disintegration and other proteinoclastic changes which take place during the first days after birth, while the newborn adjusts to the external environment and subsists on tissue reserves instead of external nourishment. Such catabolic processes are known to engender histamine-like products. Consequently the higher level of gastric acid secretory activity during the neonatal adjustment period may be construed as evidence for presence in the circulation of excessive amounts of these or related physiologic stimulants.

The Pavlov theory of acid secretion, described earlier, holds that the parietal secretion is an isotonic or nearly isotonic solution of HCl (concentration around 167 mN). None of the modern proponents[30c,48,65c] have published any special commentary with regard to the low content of free acid found in childhood, especially in the first year of life. If the theory is correct, the following peculiar circumstances must be active in all children: (*a*) the relative proportion of functionally mature parietal cells is much lower than in the adult stomach; or (*b*) the cells are not diminished in relative quantity but their *rate* of secretion is very slow, because of specific inhibition or lack of stimulation, with neutralizing secretions being formed with normal rapidity; or (*c*) the acid is being secreted at a normal rate from a full complement of cells but neutralizing mechanisms are operative to excess.

Inhibiting Effect of Fever. Yllpö[151] placed healthy infants in hot baths, which raised the body temperature to 38.5° to 40° C., and noted that the readings for hydrogen ion concentrations of their gastric juice were invariably about 1 point higher on the pH scale than before the induction of the artificial fever. A similar lessening of acidity was observed also in several vaccinated children. Daily reading of the fasting gastric contents showed a rise in the pH curves (denoting weaker acidity) reflecting almost exactly the body temperature curves. Marriott and Davison[96] found a slight reduction in intragastric hydrogen ion concentration in febrile infants ill with acute or chronic infections and Davison[32a] noted the same phenomenon in diarrhea cases. In both studies test meals of milk were employed. Bloomfield and Polland[14] describe a marked depression of gastric secretion amounting to transient complete anacidity in normal adults under artificial fever experimentally produced. The physiologic process which slows secretion of acid when body temperature is elevated has never been explained.

True Anacidity. True or complete anacidity is considered present only when no free acid is secreted following histamine stimulation. Among adults true anacidity is a chronic permanent condition. It is an almost invariable companion of pernicious anemia and occurs with great frequency in cancer of the stomach. There is a question as to how important a rôle true anacidity plays in the pathogenesis of the hypochromic microcytic anemia of middle-aged women, with which disorder it is very frequently associated. It is occasionally discovered as a random, unrelated finding in a great variety of disease conditions and occurs in many otherwise normal individuals. Distribution may be familial. Many subjects have remained entirely well over years of observation, never exhibiting evidence of gastric discomfort or disease.

Bloomfield and Polland[14] who made an exhaustive study of true anacidity

concluded that no case should be so diagnosed until certain rigid criteria had been complied with. Complete absence of free acid must be demonstrable by repeated analyses over an appreciable interval of time; temporary inhibitory influences such as fever, anxiety states and chronic infections must be excluded; histamine must not provoke secretion of hydrochloric acid, or perhaps but a trace. In most cases the gastric secretions will be found scanty in volume, rarely over 10 cc. in 10 minutes, with pH between 3 and 6, and total titrable acidity rarely exceeding 10. Only when tests for pepsin indicate that the quantity of this secretory element also has been reduced to a minimum may the designation of *achylia gastrica* legitimately be applied. With most clinically discovered cases of anacidity the histamine test, repeated if necessary, will usually bring out that the absence of acid is but false or transient.

When gastric analyses are performed on any large series of apparently normal adults, following fasting conditions, routine test meals or histamine, every possible degree of secretory activity, from none at all up to maximum rates, will be discovered. This point needs emphasis, since all evidence shows that the same sort of normal variation holds during infancy and childhood.

Instances of true histamine-resistant anacidity in childhood are rare. Insistence on refractoriness to histamine as a cardinal requirement for diagnosis excludes the data in all papers prepared prior to the introduction of the histamine test some 20 years ago,[22] as well as in many more recent publications. Indeed the number of children reported as being studied with histamine is astonishingly small in view of the great body of work which has been done on adults with this method. Dietrich and Shelby[35] studied 14 children aged 4 to 14 years and found free acid (from 19 to 117) in every case. Siemsen[128] reported on 40 tests with subjects $4\frac{1}{2}$ to 13 years of age and demonstrated strong acid responses in all but 1. This exception was a 10 year old girl, weighing 25 kg., who following the injection secreted 15 to 28 cc. every 15 minutes with 0 free HCl and 4 to 6 total acidity. The diagnosis of "undernutrition" was recorded, and the statement that the mother had pernicious anemia. No repeat tests were done, and no other comments made. Neale's[106] data is sketchy and incomplete, but he appears to have investigated 29 children ranging from 6 months to 12 years of age without encountering anacidity. Faber *et al.*[37] found no cases in 7 normal young children, 3 under 1 year of age. In Ogilvie's[108] 99 rheumatic fever children tested after porridge only 1 consistently had no acid. "The boy with rheumatism appeared to have a persistent achylia; in 6 test meals over a period of 6 months no free acid was found and the total acidity, the chlorine and the peptic activity were low even with histamine. Ventriculin and large doses of iron improved his mild anemia and general condition without having any effect on gastric secretion." Not one of 60 other healthy children between 6 months and 12 years of age tested by Ogilvie had true anacidity. Lehmann is quoted by Miller[103] as having encountered one 12 month old infant with anacidity, but the published summary[84] fails to include any reference to this case. Cutter[28] tested 72 convalescent children (36 boys and 36 girls) between the ages of 4 days and 4 years on a hospital ward, excluding any recovering from gastro-intestinal upsets and anemias. The only subjects having low values in the anacidity range were in the neonatal period: 2 prematures aged 17 and 20 days respectively, and 5 other infants aged 20 to 28 days. Repeat tests were not made. Miller[103a] had failed to find free hydrochloric acid in the fasting contents of 6 out of 50 normal newborns who were

examined daily for the first 10 days of life. Two years later[103b] 1 of these 6 babies was retested, using histamine. No free acid was produced after sufficient histamine to cause cutaneous hyperemia of head and neck. The baby's birth weight and physical development had been normal, and to all appearances he was "a strong, healthy child."

True anacidity may be adjudged, therefore, as an exceptional circumstance during childhood. Affected children have not been followed long enough to answer the question as to whether the absence of secretion will always persist as happens with mature individuals, or whether it will eventually fade away and disappear. A further problem demanding elucidation deals with the ultimate fate of these children. Are they more likely to come down with pernicious anemia or other forms of anemia than are youngsters with unimpaired gastric acid secretion?

False Anacidity. The term "false anacidity" is applied to those cases in which secretion of acid follows histamine injection, but is otherwise not demonstrable under fasting basal conditions (known also as basal anacidity) or after a test meal (relative anacidity). False anacidity happens more often than does the true or complete variety. Miller[103b] surveyed much of the published data on normal children, and noted the condition to be recorded in 100% of infants aged 2 weeks, 35% aged 4 weeks, and about 17% for ages 3, 6 and 12 months. From the first year until adolescence with the Ewald meal, there was a gradual decrease in frequency. With adults, false anacidity is often associated with gastritis. In childhood the occasional absence of free acid except on strong stimulation cannot be so readily accounted for.

Hypoacidity and Hypochromic Anemia. The close and fundamental relationship between pernicious anemia and anacidity in adults has been known for years. Pernicious anemia, of course, is encountered almost never in childhood. Another variety of adult anemia associated frequently with either hypochlorhydria or true anacidity is microcytic hypochromic iron deficiency anemia, occurring chiefly among middle-aged women. Internists suspect that some sort of unidentified gastric malfunction exists in most of these cases.[16] It is improbable that the defect lies primarily in hydrochloric acid secretion, since oral administration of this acid in abundance will not correct the anemia,[16] but rather that, as in pernicious anemia, the acid secretory defect runs parallel with the lack in some "intrinsic factor" or anti-anemic principle.

That children having the familiar nutritional iron deficiency anemia often suffer from anacidity as well has been noted by Hawksley, Lightwood and Bailey,[57] Ogilvie,[108] Faber *et al.*,[37] Paxton,[113] Stewart,[134] and Wilson.[147] With most of their patients simple test meals, but not histamine, were used for the estimation of gastric acid secretory function.

Faber[37] studied 10 children between 7 months and 2 years of age having hypochromic iron deficiency anemia and defective acid secretion. With histamine, free acid was absent in 6 and low in the remaining 4 instances; total acidity and minute-volume were low in all. Every one made a speedy recovery with iron therapy. Four of the children were soon reexamined, and still had absence of free HCl, or mere traces. Two others, twins, were only 8 months old when first seen with anacidity and anemia. Seven years later 1 had still nearly complete anacidity and a mild anemia. The other was able to produce free HCl up to 50 following histamine, and had microcytosis but no hypochromia. Faber pointed out that the average healthy child in the first few years has a mild hypochromic anemia as compared with later childhood and adult life. He suggested that the

small quantity of gastric juice with its low content of acid which is secreted normally in early childhood may handicap iron absorption and contribute to the susceptibility to nutritional anemia at this age.

Stewart[134] compared the acidity responses to the alcohol test meal among several small groups of infants. Ten anemic infants exhibited some lowering of free and total acid as compared with a control group of 7 normals, but 7 other infants having other illnesses showed a more conspicuous diminution. Three infants when tested within 4 months after recovery from anemia had low or absent free acid, but a larger series of 12 infants and young children who had been ill with anemia 7 months to 3 years earlier all showed excellent acid production. From her limited personal observations and a perusal of the papers on record, Stewart was inclined to believe that there was no evidence for the existence of a congenital failure of gastric secretion as one basis for nutritional iron deficiency anemia in infancy.

Wilson[147] reported on 12 children with nutritional anemia, 10 under 5 years of age. Six of these when tested with alcohol and histamine produced no free gastric acid; 3 others produced no acid with alcohol alone (histamine not used), and 3 had low acid with histamine. Hydrochloric acid taken by mouth for an average of 11 days while receiving a simple ward diet failed to promote significant hemoglobin rise in any patient. An ensuing course of ferrous sulfate then produced excellent blood regeneration. Gastric analyses were unfortunately not repeated after recovery. Dacie and Ellman[29] have described an 8 year old girl with good preceding dietary history whose hypochromic anemia responded quickly to iron therapy. This case is interesting because histamine-resistant achlorhydria was found to exist both before and soon after recovery; later analyses were not made.

Related mechanisms may be at work in both the nutritional anemia of childhood and the microcytic hypochromic anemia of middle-aged women, but too little is known concerning the etiology of either for clear-cut declarations to be made. The conditions differ in that true anacidity is fairly common among the adults and persists after recovery from the anemia, whereas in childhood the available facts indicate that acid secretion returns with or soon after recovery. This is illustrated by one of Ogilvie's[108] cases. A child with simple iron deficiency anemia had no free hydrochloric acid even with histamine, but 1 month later, after improvement with iron medication a simple gruel test meal elicited the production of 18 free acid.

It is not impossible that an unknown though probably insignificant proportion of children with nutritional anemia possess an underlying true anacidity—congenital perhaps—which serves as a major contributory factor in the causation of the blood disturbances, by hampering absorption of iron from the food. Nevertheless one notes that not one instance of anemia concomitant with an apparently congenital achlorhydria, established by repeated histamine tests, has been established as such by being followed over a protracted period of years.

Peptic Ulcer. During childhood chronic stomach ulcer is rare. Kraemer and Townsend[79] in 1942 were able to collect from medical bibliography but 8 instances in children between the ages of 2 and 6, and 18 cases between ages 6 and 12. Duodenal ulcer occurs 3 times as frequently.[11] Both lesions must be much more common, however, since many ulcer-bearing adults can trace their symptoms back to childhood. The few gastric analyses which are available are inconclusive and seem of little diagnostic

worth.[24,40,89,104] For example, out of Clyne and Rabinowitch's[24] 3 cases of duodenal ulceration, 1, a 13 year old girl following an Ewald test meal, had a maximum of 65 units total acidity and 45 units free acidity in $1\frac{1}{4}$ hours; another, a 7 year old boy, reached maximum levels of 35 and 20 respectively in $1\frac{1}{4}$ hours; and another 7 year old boy had peak rises to but 23 and 11 at 1 hour. Not enough diagnostic examinations of the gastric contents in gastric or duodenal ulcer are on record to furnish adequate factual basis for clinical generalization.

Free Acid in Other Disease States. With test meals average values for acid have been reported low in such conditions as asthma,[19] rheumatic fever,[108a] celiac disease,[57,108b] and anemia,[108] but the variability of individual cases has been so marked, and the number of cases so relatively small, that the statistical reliability of this supposed decrease may be gravely questioned. No decrease occurs in infantile eczema.[28,103b] In pyloric stenosis, according to Miller[103b] and Salmi,[123] gastric secretion prior to the onset of symptoms is normal in quantity and acidity. As soon as vomiting begins, gastric stasis occurs with raised free and total acidity. Later hypochlorhydria develops, though the combined acid remains persistently elevated. Steimann[133] reported on 58 children of all ages ill with a variety of diseases, measuring successive samples withdrawn through a small tube left *in situ* until the stomach had emptied. Caffeine was employed as the stimulant. Only 4 of these produced no free acid, 3 being refractory also to histamine, with recovery from their illness all but 1 began to secrete acid. Pepsin was demonstrable in 3 of the 4 at the time of transient anacidity. One only, a 10 year old girl complaining of abdominal pain, remained pepsin- and acid-free in spite of histamine stimulation. During a period of hospitalization, she exhibited no anemia or other disturbances. There is no note as to later reëxamination. Apart from anemia as discussed above, there are no known disorders of childhood in which either anacidity, hypoacidity or hyperacidity occur regularly and consistently enough to be of service as diagnostic aids.

Summary and Conclusions. Human gastric juice appears to contain no true rennin, its milk-clotting power being due to the pepsin content. Pepsin is present in indeterminate amount; it is questionable whether the pH drops low enough during infancy for its proteolytic action to be effective. Attention is directed to a newly discovered digestive enzyme, cathepsin, which appears to be of importance in protein digestion, during early childhood especially, and to the minor ferments lipase, lipokinase, gelatinase, Brücke-pepsin and the amylase-activating factor. The secretion of hydrochloric acid is low in infancy and increases with growth. In the immediately neonatal period acid secretion is temporarily increased. The fasting gastric secretion is an undependable index of acid secretory power. Carbohydrate meals of the Ewald type are moderate stimuli, alcohol somewhat stronger, while histamine provokes an excessive and unphysiologic response. Few cases are in record in which children with apparent anacidity failed to produce free acid on repeated tests with histamine. Many children with anemia have transient anacidity unless stimulated by histamine, but the deficiency tends to clear as the anemia is corrected. However there may be rare instances of anemia with complete or true anacidity in which acid is consistently absent. With healthy children the range of values for acid production is so broad, regardless of the stimulus used, that the results of gastric analyses in disease conditions are almost always worthless.

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GYNECOLOGY AND OBSTETRICS

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BENIGN LESIONS OF THE CERVIX

By Frank B. Block, M.D.

So much has been written about carcinoma of the cervix that we are apt to forget that there are many benign lesions which affect this organ. Of course, the non-malignant diseases are not apt to be lethal, except in rare instances, but they constitute a group of conditions which can be most annoying to the patient; and, if neglected, they may occasionally be a factor in the development of malignancy. Undoubtedly the most common benign lesion of the cervix is chronic cervicitis, which in many instances is the cause of a persistent leukorrhea. In order to get a cross-section of the opinions of the members of the Central Association of Obstetricians and Gynecologists, a questionnaire was sent by Kretzschmar, Randall and Brewer[11] to them; the replies showed that, in general, it was felt that chronic cervicitis is a lesion of considerable importance in relation to body functions outside the pelvic viscera, as well as being the cause of significant changes in the pelvis. A majority was of the opinion that chronic infection of the cervix can be the cause of many important symptoms. It is of interest to note, however, that chronic cervicitis was thought to be more important as a focus of infection than as an etiologic

factor in cancer. Opinion concerning their causal relation to cancer indicates that birth trauma is regarded as a much more important factor. The remainder of those replying indicated that non-specific infections rate second as precancerous lesions and specific infections third. Questions relative to the investigation of cervicitis revealed that the majority did not feel that smears were important and that biopsy was indicated in only a few cases. Most of the men were of the opinion that the Schiller test and colposcope added little to the investigation of this condition. It would seem, therefore, that, in general, gross inspection of the lesion was thought to be adequate to make the diagnosis and to decide on proper treatment. By far the most common form of treatment used is actual cautery. The next in order of frequency are the 3 operative procedures: Sturmdorf amputation, trachelorrhaphy, and conization, which occupy about comparable positions. Cautery with chemical agents occupied a position quite similar to these 3 procedures, and cautery under anesthesia is next in importance. The incidence of complications following treatment was surprisingly large. An analysis of the 3 chief complications, hemorrhage, stenosis and infection, revealed that cautery was responsible in 35%, 38%, and 54%, respectively. Since there has been considerable discussion concerning the relative merits of conization and Sturmdorf amputation, a comparison of complications following these was thought desirable. It was noted that the total number of complications was about the same. There is a higher incidence of hemorrhage and infection with conization, while the incidence of stenosis of the cervix following the Sturmdorf operation is sufficiently high almost to equalize this. In view of the large number of complications reported, it is of interest to study the opinion concerning contraindications to treatment. It was noted that retroversion which has been emphasized by many as a contraindication was regarded as insignificant by 80% of those replying. The fact, however, that 97% avoided treatment in active infection and yet 148 acute infections attributable to the treatment were reported, suggests that the method of diagnosis of infection of the upper genital tract or its activity may be lacking in efficiency.

Until comparatively recent times cervicitis was treated by a variety of douches and the application of medicines by means of tampons; but since the effect of such treatment was only upon the superficial cells, it has been largely replaced by various forms of cauterization. At the Mayo Clinic, according to Piper,[14] of 640 patients whose cervices had been cauterized and who replied to questionnaires 6 to 9 years after treatment, 1 patient only reported the development of cancer. That patient had had a polyp removed and its base seared by the cautery. She was treated elsewhere for epithelioma of the cervix 4 years later. That chronic cervicitis is a source of infection is demonstrated by the relief of chronic backache, and also by the improvement in the sensation of pelvic heaviness, in some malpositions of the uterus and in tenderness of the uterine ligaments after application of cautery to the cervix. In a series of cases from the Clinic of 358 patients who have had an associated lumbosacral type of backache 62.8% were relieved and 11.4% reported the backache improved.

The results of treatment of 611 patients at the Hospital of the University of Pennsylvania have been presented by Tompkins.[16] The methods of treatment were cauterization, trachelorrhaphy, Sturmdorf operation and amputation. Each method gave relief of leukorrhea in approximately 85% of cases. Trachelorrhaphy gave a lower percentage

of complete cure of leukorrhea and effected cure more slowly than other methods. Approximately 66% of married women in the childbearing age who had previously borne children conceived after each type of cervical repair. Approximately 50% of married women in the childbearing age who had never been pregnant conceived after cervical repair. Two patients among 611 who were traced after the repair of benign lesions of the cervix subsequently developed cervical carcinoma. The most important factor in the relief of leukorrhea due to cervicitis is the selection of a type of treatment suitable to the individual case. Approximately 85% of patients will be relieved of leukorrhea if the choice of treatment is based upon proper indications. In general trachelorrhaphy cannot be recommended as a satisfactory procedure when the principal object of treatment is complete cure of leukorrhea. The possibility of producing cervical stenosis which will interfere with conception should not influence the choice of treatment for benign lesions of the cervix.

A message of caution is offered by Cannell and Douglass[4] that the occurrence of widespread pelvic infections following cauterization is evidently much more frequent than is commonly supposed. The presence of a latent gonorrheal infection of the cervix should be carefully eliminated wherever possible. Patients with a history of infected abortion, especially of recent occurrence, should be dealt with most cautiously as subjects for cervical cauterization especially with heavy duty or Paquelin cautery. An instance of pelvic inflammatory disease has been observed, apparently immediately initiated by office cauterization for erosion of the cervix in a patient with adherent retroversion of the uterus and one-child sterility of 7 years duration. This patient had had a number of negative smears and had no local stigmata of gonorrhea. These cases suggest that the cautery should be employed with extreme care and circumspection and with the knowledge that severe cellulitis may result occasionally as a complication.

One of the popular methods of attack for the removal of diseased cervical tissue is that known as conization which consists of the removal of a cone of cervical tissue by means of the high frequency current. Based on an experience of about 900 of these operations Miller and Todd[13] state that they prefer to hospitalize every patient for 3 or 4 days. When the cutting current is properly combined with coagulation, the operation becomes a bloodless procedure—and in this respect is in striking contrast to most cervical amputations, particularly the Sturmdorf operation. It takes about 6 weeks for complete epithelization to occur following conization. It is their custom to guard against stricture during this time by placing an iodoform wick in the cervical canal at the time of operation in all patients except those who are to have a sub-total hysterectomy. This wick is removed on the 3d day and the patient is discharged with instructions to take a daily cleansing douche and report bi-weekly for check-up examination. At this time the cervix is painted with an antiseptic and a sterile sound or hemostat is passed into the canal. This procedure is repeated at 2-week intervals until epithelization is complete. After years of experience and careful follow-up of their cases, they feel that extensive conization is not to be viewed as a substitute for simple cauterization, coagulation, or other valuable means of treating benign cervical disease. On the other hand, the benefits from extensive conization are real, and it should have a place in every-day gynecologic surgery. The indications for using this method of treatment, in their opinion, are (1) As a means of correcting minor cervical disease and preventing remote complications of the cervix, in patients for whom sub-total hysterectomy is planned. (2) As a means

of eradicating deep-seated chronic infections of the cervical canal in older women. (3) As a complete substitute for the Sturmdorf operation in any condition of the cervix for which the Sturmdorf operation is indicated. (4) As a means of obtaining adequate biopsy material in cases in which original biopsy material presented cytologic abnormalities strongly suggesting neoplastic change. (5) As a substitute for older methods of trachelorrhaphy in most women but especially in elderly women. Extensive conization as here described is a hospital procedure and should be reserved for the more severe types of cervical lesions. No serious immediate complication occurred in any of the conizations comprising this study. During the first few days there is little discomfort but commencing the 3d or 4th day the discharge becomes profuse and is often bloody. Normally this discharge persists for 2 weeks, after which it gradually decreases. Vaginal cleansing douches are essential during this healing period, the type of douche making but little difference. Ultimate healing with complete epithelization renders the cervix clean and normal in appearance. In a few patients small areas of delayed epithelization are noted. In these, healing may be hastened by the use of the fine nasal tip cautery. Strictures occurred in about 9% of the cases. The majority were mild and required only dilatation or passage of a sterile sound or hemostat. The fact, however, that strictures do occur, some of them severe, warrants care in the selection of cases and careful observation afterward. While the number of pregnancies subsequent to conization in this series is small, the trend certainly suggests a harmful influence on subsequent pregnancies. This is seen to be in the direction of abortion and premature labor rather than cervical dystocia as might have been anticipated. This tendency to early interruption of pregnancy is another drawback and suggests its use only in women past the childbearing period, and even then they do not consider it a substitute for the less radical office procedures in mild cervical disease.

A method of chemical cauterization using zinc chloride without the necessity of an anesthetic has been reported by Bourne, Bond and McGarrity.[2] Porous clay pencils were used as the medium for introduction. They were 1½ inches long and of different diameters. If these pencils are placed in a saturated solution of zinc chloride for 10 minutes, they will become fully charged with the salt and ready for use. In most cases there is no difficulty in inserting one of a suitable size without pain, and it is easy to remove by the wire passed through a hole drilled in the proximal end of the pencil. The absorption of zinc chloride by the tissues is fairly constant according to the size of the pencil and the duration of the application and it is sufficient to produce necrosis of the mucosa extending from about 2 to 4 mm. deep. If the dose of zinc has been insufficient, either because too small a pencil has been used or because the time of application is too short, the zone of necrosis will be uneven or not deep enough to affect all the glands, and partial failure will follow; on the other hand, if the dose has been excessive, necrosis may penetrate too deeply. In these cases a large slough, representing a cast of the major part of the cervix, tunneled by its canal, may separate about the 7th day, but even though so much tissue has been removed they have never seen anything more than very slight bleeding at the time of separation. The type of cervix most suitable for treatment by zinc chloride is the one that has not been deeply lacerated and is therefore able to hold the pencil in close contact with its wall throughout its whole length. A strip of gauze moistened with a 5% solution of sodium bicarbonate is loosely packed around the

cervix and firmly against the os to maintain the pencil in position. The pencil is withdrawn in from 2 to 4 hours, depending on its size. No further treatment is necessary. The subsequent clinical course is as follows: For 2 or 3 days there is no discharge; this is due to the complete necrosis of the mucous membrane, which has not yet begun to separate as a slough. About the 3d or 4th day it reappears and increases until the 6th or 7th day when a little blood is usually noticed. This corresponds to the separation of the necrotic mucosa as a slough either in one well-defined gray mass or in the form of small particles and shreds. For a few days there is a profuse seropurulent discharge, which gradually diminishes during the next 4 weeks until finally there is nothing more than the normal moisture of the vagina.

The use of ionization in the treatment of chronic cervicitis has been very encouraging to Forman[8] who has treated 93 patients and given 389 treatments. Of these, 71 patients were discharged as completely cured. There were 6 complete failures; these patients had a pelvic inflammatory disease with a palpable mass confusing the picture. Seven patients after receiving the full course of 6 treatments were relieved of the profuse discharge, but, clinically, were not cured, a definite erosion with edema of the cervix being present.

Method. The technique employed is as follows: The ionization apparatus delivers a direct galvanic current which is controlled by a rheostat and measured by a milliampere meter gaged to 25 milliamperes. The instrument has two poles The negative one is attached to a specially designed indifferent electrode covered with a wet felt pad. To the positive pole is attached the intracervical copper electrode which is made in 5 sizes, designed to fit the cervical canal without entering the internal os. The wet felt pad connected to the negative pole is placed under the buttocks of the patient. A bivalve speculum is then introduced, the cervix exposed, and secretion removed. The proper sized copper electrode is inserted to the internal os. If the external os is too small to admit even the smallest electrode, the tip of the electrode is introduced and the negative current is turned on slowly. Five to 10 milliamperes used for about 5 minutes causes softening and relaxation of the tissues about the external os, permitting the further insertion of the instrument. After the electrode his been properly placed, the positive current is turned on, the rheostat is turned slowly until the milliameter registers from 8 to 20 amperes, depending upon the amount of current desired. The larger the area of the electrode in contact with the cervical canal, the greater the amount of current. After a minute or two, the electrode adheres to the cervical mucosa. Cotton is then packed against the cervix surrounding the electrode to prevent its displacement. At the end of 15 or 20 minutes, crystals of copper oxychloride may be seen to surround the electrode and external os. The current now is turned off slowly, the electrode withdrawn, and the cervical canal is seen to be covered by a layer of copper crystals. Very often, due to superficial electric coagulation and dehydration of the tissues of the cervix, the electrode becomes adherent to the cervical mucosa. This necessitates the use of the negative current for 2 or 3 minutes in order to allow the withdrawal of the electrode without undue trauma to the cervical mucosa. The patient is then instructed to take a cleansing douche every night and to return in 2 weeks for another treatment; 4 to 6 such treatments are usually sufficient in clearing up the average case of endocervicitis with erosion. Most patients have complained of some degree of cramplike pain in the lower abdomen during and for several hours after the treatment. In a few cases the pain was severe enough to confine them to bed for 1 day, but no other untoward effects were noted. In no case has there been any evidence of bleeding or slough. His experience with this method leads him to believe that it approximates, more closely than any other thus far advocated the ideal treatment for endocervicitis. The deposition of copper as copper oxychloride produces a marked bactericidal effect. The mild coagulating property of the positive current causes a shriveling and obliteration of the infected glands, while the technique of treatment keeps

the cervix well dilated, bring all the mucosa and the openings of the cervical glands in contact with the electrode and, what is more important, permitting adequate drainage.

Stricture. In one of his characteristically instructive papers Curtis[6] states that the frequency of cervical strictures merits repeated emphasis; they are of common occurrence in the practice of everyone concerned with pelvic diseases of women. The various therapeutic procedures employed in the treatment of lesions of the cervix are more important than any other factor in the etiology of cervical obstructions. Endocervicitis is also important in the etiology, and in the majority of cases of serious stricture there is a history of an inflammatory process as well as of instrumentation. It must not be assumed, however, that absence of a history of infection or of instrumentation invariably gives assurance of a patent cervical canal and adequate uterine drainage. Marked strictures are encountered in virgin patients and in others in whom there is no discoverable predisposing factor. Fibrotic constriction of the cervical lumen is much more serious than simple obstruction by adhesions. If drainage is not free, pocketing of the cervix may occur immediately above the fibrous obstruction. Metaplasia of the columnar epithelium into squamous epithelium has been found in the roughened pocketed endocervix above a cervical stricture. Irritation from retained secretions may be a factor in stimulating the metaplasia. Tumorous nodulations of the endocervix and lower uterine segment are a less common cause of uterine obstruction. The effects of damming back of uterine secretions and menstrual blood may be far reaching—perhaps important in the etiology of endometrial polyps, adenomyosis of the uterus, pelvic endometriosis, and back pressure inflammatory processes in the pelvis. The relationship of obstructive retention to the development of intra-uterine cancer is a problem which merits further study. He believes it will eventually be regarded as a surgical sin to use radium, or make repeated endocervical topical applications, or apply the cautery within the cervical canal, or amputate the cervix of the uterus, or even administer expectant care to a patient with notable endocervical disease, without prolonged and attentive observation thereafter directed to the maintenance or patency of the cervical canal. Our thoughts have been too little concerned with the lumen of the uterus and the importance of free uterine drainage.

Reviewing the ultimate results in a series of 261 patients operated upon at Woman's Hospital, New York, for chronic cervicitis, Bullard[3] finds that for the cure of cervical leukorrhea high amputation is perfect, Sturmdorf operation excellent, low amputation very good, and trachelorrhaphy disappointing. Varying degrees of cervical stenosis followed high amputation in 54% of the cases, low amputation in 18%, trachelorrhaphy in 12%, and Sturmdorf tracheloplasty in 1.8%. Of 59 cervices repaired by high amputation, 23 were impenetrable by a probe, yet only 2 had obstructive dysmenorrhea. Only 2 out of 59 operated upon required operative dilatation later. There was much less stenosis after low amputation (18%), only 2% had obstructive dysmenorrhea while there was no obstructive dysmenorrhea after trachelorrhaphy. The Sturmdorf operation gets a well-nigh perfect record of non-interference with subsequent pregnancies and labors. One case of serious cervical dystocia followed a unilateral trachelorrhaphy, and this type of operation may have caused a premature labor in another; but there were 9 entirely normal labors in patients who had a previous trachelorrhaphy. No dystocia and no abortions followed low amputations, and there were 8 normal labors; but this

operation was the cause of at least 1 premature labor and perhaps of 3 others. Of 4 pregnancies after high amputations 2 terminated in premature labors and 2 aborted from undetermined causes, a bad record. Diathermy may replace surgery in the treatment of chronic cervicitis; but only if it will eradicate the entire diseased area as dependably as a knife and show a better record in subsequent labors than the Sturmdorf operation. The degree of scarring following diathermy has not been sufficiently demonstrated.

The Retained Cervix. For many years there has been discussion among gynecologists as to the advisability of removing the cervix in all cases where hysterectomy is performed. Those in favor of complete hysterectomy base their opinion on the danger of the development of carcinoma in the retained stump. A study which has been made by Henriksen[9] is of interest because while he shows that the incidence of cancer is low, there are other symptoms which develop in a small percentage of patients whose cervix is retained. The alteration in the vascularity of the retained cervices, together with the loss of the changes in diameter of the cervical canal which normally accompany menstruation, tend to stricture formation, with subsequent cervical pyometra. These strictures and abscesses are often overlooked in routine examination, especially when the portio vaginalis presents a grossly normal smooth surface and a small external os. Not infrequently it is this type of cervix that constitutes the causative source of backaches, urinary symptoms and a persistent leukorrheal discharge. Simple dilatation of the cervical canal usually results in quick relief. In a series of 6550 stumps, he has records of 157 patients returning because of complaints relative to the stump. Of the 157 patients, 26 were found to have primary carcinoma of the stump.

The common cause of periodic vaginal bleeding following sub-total hysterectomy is high amputation of the corpus, and the bleeding is therefore an indication of menstrual activity. Of 22 patients presenting irregular vaginal bleeding, 7 had definite malignancy of the stump. This is the most dangerous group in the series. Patients are frequently advised not to be alarmed if they experience scant bleeding on several occasions following sub-total hysterectomy. Naturally, the patient is likely to interpret such bleeding when it does occur as of no importance. Again, not infrequently abnormal bleeding may even appear several years following the operation and may then be considered as an indication of the menopause. The patients in this group in whom benign lesions were found, presented for the most part functioning endometrium in association with chronic infections of the cervix or cervical polyps and were treated by cervical cauterization. Of the 32 patients complaining of an inoffensive vaginal discharge, varying in amount from a self-termed "moderate" to "profuse," 3 had cancer of the stump. Six of the 19 patients presenting a foul discharge and no evidence of bleeding were found to have cancer. There were 20 patients complaining of vaginal discharge with various degrees of bleeding; 9 of these had cancer of the cervical stump. Many of these patients who complain of leukorrheal discharge in the absence of cancer show definite evidence of stricture about the external os, in spite of the presence of deep lacerations. He treats these strictures by dilating the canal to the size of a No. 12 Hegar dilator, generally this is more efficacious than the cautery, but care must be taken not to tear the cervix during the insertion of the dilators. The fact that only 2.4% (157 patients) of the 6550 patients returned to the hospital with complications referable to the stump, and that of these he has records of only 26 or a percentage

of 0.45 showing cancer, indicates that the incidence of stump cancer is so low as to be of relatively little import. There is no evidence that subtotal hysterectomy predisposes to cancer of the stump or that the residual stump is more susceptible to malignant changes than the cervix of a complete uterus. He does not feel that the 0.45% incidence of stump cancer is sufficient reason to advise the total operation with its morbidity-mortality rate of 2 to 5%. It is common knowledge that in the hands of the less experienced surgeon, total hysterectomy is accompanied with greater risk than when the more conservative operation is employed. The more rational approach would be to fit the operation to the patient and to the physical findings, rather than to advocate either operation as a routine. With proper pre- and postoperative treatment of the cervix, total hysterectomy merely as a prophylactic against cancer of the stump is probably rarely indicated.

The development of a fibromyoma in the cervical stump following hysterectomy is very unusual. Based on an experience of 4 such cases Hyams[10] states that these tumors grow more rapidly than those of the body of the uterus and may attain a considerable size. The majority originate in the posterior portion of the cervical stump and tend to grow backwards toward the cul-de-sac. They may be retroperitoneal, intraligamentary, or subvesical. The first manifestations are usually obstructive, due to pressure of the growth, and consist of marked constipation, pain in the abdomen or pelvis, and if adhesions are present, drag on the adjacent viscera. With pressure on the bladder, the patient complains of urinary disturbance, urinary frequency, urgency, incontinence, or retention. Vaginal bleeding or discharge is frequently present; it may be slight or profuse. In 1 of his patients, the bleeding was so severe that immediate transfusion was necessary. If the possibility of such a tumor is borne in mind, the diagnosis should not be difficult. It is based on palpation of a solid tumor attached to the cervical stump. If the mass fills the pelvis, there may be some confusion as to the origin and type of tumor, particularly if the uterine adnexa have not been removed or dense adhesions are present. Because of the location of the growth and possible distortion of the ureters or bladder, a careful urographic study of the urinary tract should be made to determine the relation of these structures to the tumor before treatment is instituted. Surgical intervention should be prompt. Because of the site of the growth and its tendency to grow upward and backward, the abdominal route offers the best method of approach. The operation may be difficult and tax the skill of the surgeon, as dense adhesions usually present may cause malposition, distortion or fixation of the adjacent structures. Once free, the tumor is easily shelled out. The possibility of distortion of the bladder from a previous operation or possible atypical position of the ureters should not be overlooked, and care must be taken in the identification, separation, and preservation of these structures. If the tumor mass is found so adherent to the bladder that separation cannot be accomplished without injury to the viscus, it is advisable to resect that portion of the bladder with the tumor mass, and repair the opening in the bladder wall. There is usually considerable venous oozing from the cavity from which the tumor is enucleated and this is best controlled by packing. All raw areas should be peritonized.

Tuberculosis. While all investigators admit that tuberculosis of the cervix is a rare disease, it merits consideration because of its clinical resemblance to carcinoma. In a report based on 191 cases Collins[5] states that in approximately 85% of the cases it is secondary to a tuberculous

focus found in the lungs or in either the gastro-intestinal or the genito-urinary tract. Of the 185 cases which he has studied from the literature, in 156 (84.3%) there was demonstrable tuberculosis elsewhere. In 102 cases (55.1%) genito-urinary tuberculosis was present in either an active or a quiescent stage. Marriage and pregnancy are two common contributing etiologic factors. Tuberculosis of the female generative tract occurs most frequently in the Fallopian tubes and progressively diminishes in frequency as it approaches the uterine cervix. It is believed that this disease usually results from a descending infection spread by contiguity from foci situated higher in the pelvis or by hematogenous and lymphogenous routes from distant foci. Primary tuberculosis of the uterine cervix is rare. In this series of 185 cases studied from the literature there were 16 proved instances of this type of primary infection. A true example of primary tuberculosis of the uterine cervix must fulfil the criterion of being the only focus of tuberculosis in that patient. Tuberculosis of the cervix uteri is classified into 4 types: the ulcerative, the papillary, the miliary and the rare bacillary catarrhal. Thus the gross appearance of the cervical lesion may vary widely. The typical lesion is usually ulcerated. The edges are either well defined or undermined and are surrounded by either tubercles or normal-appearing tissues. The adjacent portions of the vagina may be involved, and tubercles may be seen. Secondary infections are commonly superimposed on these lesions. Varying degrees of bleeding or even severe hemorrhages with accompanying foul leukorrhea are frequently encountered. Microscopically, typical tubercle formation is commonly seen. Often atypical tubercles composed of only epithelioid and lymphocytic cells may be the only evidence on which a presumptive diagnosis of tuberculosis can be made. Acid-fast stains for the presence of the tubercle bacillus in either the microscopic section or the tissue smear may be apparently negative. Inoculation of guinea pigs may prove to be the only reliable method by which a correct diagnosis can be established. Biopsy is a quick correct method of establishing a probable diagnosis. Removal of such a specimen will not injure the patient, while the issues at stake are of such gravity as to make a correct diagnosis imperative. The treatment of tuberculosis of the uterine cervix should preferably be of radical surgical character, such as abdominal panhysterectomy with the possible preservation of one ovary, if the patient's condition and other factors are favorable, because usually extensive tuberculous disease of the upper pelvic part of the generative tract is present and must be eradicated if cure is to result. For that reason and because of the rarity of a primary tuberculous infection of the cervix, local treatment of the cervical lesion is not advisable. For similar considerations Roentgen and radium therapy will often prove to be disappointing in their end-results. The contraindications to the employment of surgery are advanced local tuberculous lesions with extensive involvement of the neighboring bladder or rectum, extensive tuberculous salpingitis, marked secondary infection, the presence of active tuberculous foci elsewhere, cardiovascular disease and senility.

At Peiping, Lin[12] found 21 cases of pelvic tuberculosis over a period of 15 years. He found that it occurs most frequently during a period of sexual activity and may be due to either exogenous or endogenous infection. It produces no pathognomonic symptoms although menstrual disorders, hemorrhage, leukorrhea and sterility are common complaints. The disease is frequently confused with cancer and the definite diagnosis can sometimes be made only by microscopic examination. The treatment

depends on whether the disease is primary or secondary in the cervix. If primary, radical surgery is indicated, but if secondary, often associated with tuberculosis in the lungs, tubes and ovaries, palliative local treatment is probably the wisest procedure.

Danforth[7] concurs with the preceding authors that in the great majority of cases it is secondary to tuberculosis at higher levels of the genital organs which in turn are usually preceded by lesions elsewhere, usually in the lungs, from which the tubercle bacilli find their way to the pelvis *via* the blood stream. Infections from external contact are rare. The symptoms are usually not marked and consist largely of leukorrhea. The disease is frequently mistaken for cancer although the typical induration of cancer is absent and the lesion does not bleed as easily on contact. He states that radiotherapy should not be used but the best treatment is complete hysterectomy if the condition of the patient permits. If it is quite certain that tuberculosis of the cervix is primary, amputation of the cervix will be a satisfactory operation.

Granuloma Venereum. Another benign lesion which may be confused with carcinoma is granuloma venereum, also known as granuloma inguinale. The recognition of this disease in the cervix is comparatively recent since Pund, Huie and Gotcher[15] were unable to find a single case of granuloma venereum of the cervix in the files prior to 1934. However, since 1934 9 cases were observed and this confirms the impression that venereal granuloma is on the increase. The 9 cases were found in the 830 biopsies of the cervix which were performed between Jan. 1, 1934, and March 31, 1938. This is 1.1% of all cervices that were biopsied. Of these 830 patients, 694 were white and in none was the diagnosis of granuloma venereum made. Of the biopsies from the 136 negro patients, 9 were positive for granuloma venereum, an incidence of 6.6%. If the 69 carcinomas are eliminated from this group, we find that 13.4% of the remaining 67 negro patients who complained of cervical lesions, suffered from granuloma venereum.

In an analysis of 38 cases of this disease Arnell and Potekin[1] state that it is now generally agreed that granuloma inguinale should be regarded as a venereal infection, even though extragenital lesions have been described. The Donovan body, which is the specific etiologic agent in granuloma inguinale, is a microörganism which probably belongs to the protozoan group, although there is some evidence to suggest that it may be a fungus. It is pathogenic only for man and is transmitted only by direct contact. It has never been cultured. The incubation period is thought to be 40 to 60 days. The lesion of granuloma inguinale of the cervix appears first as a soft, red, granular macule. It enlarges rapidly and sometimes ulcerates early, forming a shallow, granular ulcer with well-defined edges. Sometimes it develops as a hypertrophic granular mass in which are numerous small areas of ulceration. In advanced stages the entire cervix may be replaced by a large cauliflower mass of soft, friable bleeding tissue. The cervical lesion may extend to the adjacent vaginal walls and may completely fill the vaginal vault, or, occasionally, may be combined with only a few discrete vaginal lesions, or even a single lesion. Microscopic examination of the lesion reveals characteristic exuberant granulation tissue in which the pathognomonic cell is found. The essential feature of the histopathology is the presence of large monocytes with many intracytoplasmic spaces in which the Donovan bodies are dispersed. These bodies, which are elliptical or round and stain deeply, are usually arranged peripherally in the intracytoplasmic

spaces. Sometimes, however, they are scattered through the cell, or appear as one or more collections, pushing the nucleus to the side. Of the 38 patients, 34 were colored and only 4 white, these figures being in agreement with the high proportion of negroes with granuloma inguinale of the external genitalia reported in the literature. Apparently these are the first cases of cervical granuloma inguinale to be reported in white women. A purulent or bloody vaginal discharge, hemorrhage, and pelvic pain were the chief complaints for which the patients sought relief. The earliest symptom was usually a serous discharge, followed successively by purulent leukorrhea, blood-stained leukorrhea, or in some instances, by profuse vaginal hemorrhage. Bleeding was present in 31 of the 38 cases, the prominence of this symptom being due to the tendency of the lesion toward early ulceration, with involvement of the highly vascularized cervical tissue. Thirty patients complained of pain or discomfort in the lower abdomen, usually associated with backache. The pain was bilateral in all but 4 instances. Many patients exhibited parametrial and adnexal thickening and tenderness upon pelvic examination, and 8 had palpable masses in the pelvis. In many, if not in most cases the pelvic inflammatory disease was concomitant or preëxistent, and not the result of the cervical infection, for a large percentage of the colored women treated at Charity Hospital exhibit pelvic disease. In other instances the associated pelvic disease was apparently due to secondary infection of the primary cervical lesion, with lymphatic extension to the pelvis. Direct extension of the granuloma inguinale to the pelvis may also occur, with involvement of the uterus, tubes and ovaries. Ten of the 18 patients who were hospitalized had temperatures above 100° F., and 14 had sedimentation rates of less than 30 minutes. Many were anemic and complained of weakness, thus demonstrating the effects of blood loss and of chronic infectious processes. The duration of symptoms varied from 1 week to 3 years. Most of the long-standing cases represented untreated or chronic lesions, or perhaps recurrences, rather than reinfections. About one-half of the patients sought relief in less than a month after the onset of symptoms, apparently because of the foul-smelling, sanguinopurulent discharge which caused sufficient discomfort to force them to seek early medical consultation. The interval is unusually short for colored patients who tend to delay medical consultation whenever severe pain is not a prominent symptom. Antimony compounds are considered specific in granuloma inguinale and should be employed routinely, although, if special indications are present, it may be necessary to employ other measures also. They prefer tartar emetic to fuadin. It is given intravenously twice or 3 times a week, in doses of 10 cc. of 1% solution. Local therapy is also advised in all cases. They have had the best results with topical applications of neoarsphenamine (4.5%) in glycerin to combat fusospirochetosis and secondary infections and to promote healthy granulation tissue. They also employ potassium permanganate irrigations (1:1000 solution) to alleviate local irritation and to overcome the odor of the discharge. In most cases clinical improvement was noted within 3 to 4 weeks after treatment was begun. In 1 instance cure was effected by 4 injections of tartar emetic given over a 4 weeks period, but the average duration of treatment was 3 months. The longest course of treatment was 14 months. It is most important that treatment be continued long enough to effect a permanent cure; the tendency is to discontinue it when signs of superficial improvement are evident. Chronic lesions are often resistant to therapy, but early lesions usually respond rapidly, and prompt

diagnosis is therefore essential to a rapid cure. Recurrences with any form of therapy are unfortunately common. The therapy of granuloma inguinale of the cervix during pregnancy demands a special note since the response to tartar emetic therapy is poor. Large growths may complicate labor and introduce serious hazards of hemorrhage and infection. Delivery from below should always be employed if it seems safe. If, however, the cervical growth is extensive or if concomitant lesions of the external genitalia have produced so much scar tissue that vaginal delivery seems unwise, Porro Cæsarean section may be necessary.

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PHYSIOLOGY

PROCEEDINGS OF
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The Incidence of Hemolytic Anemia in Mice Fed Diets Containing Sulfamerazine, Sulfadiazine, or Sulfapyridine. ALBERT R. LATVEN and ARNOLD D. WELCH (Department of Pharmacology, Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa.). Hemolytic anemia is occasionally seen when sulfonamides are administered to man. In the mouse, however, an anemic condition of the hemolytic type has been shown to develop within a period of 2 weeks when sulfanilamide, sulfanilylguanidine, sulfapyridine or sulfathiazole is incorporated in the stock ration. The potentiality of each of these drugs for the production of anemia was related by Richardson (*J. Pharmacol. and Exp. Therap.*, **72**, 99, 1941) to the sulfonamide concentration found within the erythrocyte; the 4 sulfonamides were shown to be indistinguishable from one another with respect to the molar erythrocytic concentration required to produce anemia.

In this study, sulfamerazine and sulfadiazine were examined for their capability of producing hemolytic anemia in the mouse; sulfapyridine was used as a standard of comparison. The sulfonamides were thoroughly incorporated in the stock ration in various concentrations, each of which was given *ad libitum* to several experimental groups. Evidence for the production of anemia was obtained from colorimetric determinations of hemoglobin, using the acid-hematin method.

The comparison of the anemia-producing potency of the sulfonamides was based upon the percentage incidence of anemia at various levels of sulfonamide concentration in the blood. The blood level which produced a 50% incidence of anemia was found to be as follows: sulfapyridine, 2.8 mg. per 100 cc.; sulfadiazine, 33 mg. per 100 cc.; and sulfamerazine,

31 mg. per 100 cc. The actual sulfonamide concentration within the erythrocytes at these levels was: sulfapyridine, 2.5 mg. (10 micromols) per 100 cc.; sulfadiazine, 26 mg. (105 micromols) per 100 cc.; and sulfamerazine, 23 mg. (87 micromols) per 100 cc.

Although Richardson's findings with sulfapyridine have been confirmed, the 2 pyrimidine derivatives, sulfamerazine and sulfadiazine, are productive of hemolytic anemia in the mouse only when the sulfonamide concentration within the erythrocytes is raised to a level approximately 10 times that required for sulfapyridine. Although it is possible that the degree of hemolytic anemia produced in the mouse by a sulfonamide may be related to its concentration within the erythrocyte, it is apparent that the various sulfonamides are not necessarily equivalent in anemia producing potency and that the toxic effect of sulfonamides on erythrocytes is not inherent in the sulfanilamide nucleus. Clinical data so far available suggest that the incidence of hemolytic anemia in man following the use of sulfadiazine or sulfamerazine is lower than with sulfapyridine or sulfathiazole.

Effects of Acute Hemorrhage of Known Amount on the Circulation of Essentially Normal Persons. H. A. SHENKIN, R. H. CHENEY, S. R. GOVONS and I. STARR (Departments of Neurosurgery and Research Therapeutics, University of Pennsylvania). A group of 23 essentially healthy volunteers has been bled amounts which varied from 500 to about 1000 cc. Observation of pulse rate and blood pressure were made, before and for several hours after hemorrhage, in both the recumbent and erect positions; and ballistocardiograms were taken in the recumbent position. When the amount bled was over 500 cc. the blood drawn was eventually replaced and observations made after its restoration. The blood was drawn from the antecubital vein in from 4 to 20 minutes.

Hemorrhages up to 1000 cc. produced only slight changes of blood pressure, pulse rate and ballistocardiographic record as long as the subjects remained recumbent. The values obtained were usually well within the normal range, so that in the great majority of cases it would have been impossible to diagnose the hemorrhage, had one not been aware of it, as long as the subjects remained recumbent and at rest.

However after the hemorrhage as soon as the subjects stood upright the pulse rate accelerated and blood pressure fell to a degree far more marked than was found either before the hemorrhage or after the blood was restored, and 8 subjects were unable to stand without collapsing. Such spells of faintness were accompanied by marked slowing of the pulse, sweating, facial pallor, and nausea, which sometimes persisted for several minutes after the subject was laid flat.

Conclusions. Hemorrhage of large amounts could not be diagnosed by the usual clinical methods as long as the subjects were recumbent and at rest. But as soon as the subjects arose, the abnormality became apparent.

A Biological Method for the Quantitative Estimation of Certain Organic Bases. DOROTHY R. STEWART and M. H. JACOBS (Department of Physiology, University of Pennsylvania). The method depends on the ability of tannic acid (*a*) to combine with alkaloids and other organic bases, and (*b*) to retard the exchange of ions across the red cell membrane, thereby slowing the course of hemolysis in a suitable mixture of NH_4Cl and NH_4HCO_3.

The pH of a M/6 solution of NH_4Cl is first raised slightly above 7, with an alkaline phosphate buffer and approximately M/600 NH_4HCO_3 and 1/600% tannic acid are added. The times of 75% hemolysis of freshly washed erythrocytes in this mixture are then determined (*a*) with no addition, (*b*) with the addition of an unknown amount of the base in question, (*c*) with the addition of known amounts of the same substance, and (*d*) with the omission of the tannic acid. To secure speed as well as accuracy, the unknown concentration is adjusted by dilution to give a time of hemolysis 2 or 3 times as great as that obtained with the test solution lacking the tannic acid.

Since tannic acid also combines with proteins, which begin almost immediately to escape in disturbing traces from freshly washed erythrocytes, standardizations and measurements are carried on simultaneously, using 3 tubes at a time, all started at the same instant, the middle one containing the unknown solution and the others one of a higher and one of a lower known concentration respectively. By a series of successive approximations the known solutions are brought to any desired degree of closeness to each other and to the unknown solution.

The method has been tested superficially with quinine and strychnine and carefully with atabrine. With the latter substance concentrations of 1 to 1 million or less can be measured with an accuracy of 2 or 3%.

Respiratory Inhibitions Studied by Analysis of Single Fiber Discharge in the Phrenic Nerve. ROBERT HODES and M. G. LARRABEE (Johnson Foundation, University of Pennsylvania). The superior laryngeal nerve was stimulated centrally in anesthetized cats and the activity in single phrenic motoneurones was recorded by means of an amplifier and cathode-ray oscillograph.

A sharply defined threshold for inhibition of inspiration can be demonstrated by applying different numbers of stimuli during the course of inspiration. With stimulation of less than threshold value, short delays are introduced between successive phrenic impulses, after which inspiration continues to completion. The greater the sub-threshold stimulation applied, the greater is the pause between successive phrenic impulses. Threshold inhibitory stimulation frequently causes a sequence of events consisting of the customary cessation of activity during stimulation followed by escape of 1 to 3 impulses before inhibition becomes complete. This brief resumption of activity may occur following stimulation during the middle or latter part of inspiration but is never seen following stimulation applied immediately after the first impulse of an inspiration.

The threshold for inspiratory inhibition declines progressively during the course of inspiration. Two periods of subthreshold stimulation can sum to inhibit inspiration when separated by as much as 0.4 second.

Brief stimulation during expiration prolongs the expiratory phase.

All the above results can be demonstrated after section of the carotid sinus and vagus nerves.

Inhalation of high CO_2 or low O_2 mixtures raises the inhibitory threshold. The response to high CO_2 remains despite chemoreceptor denervation, but the low O_2 effect is abolished by such a procedure.

All the foregoing results, as well as most other respiratory phenomena can best be explained by employing, with a few additions, the schema of respiratory interconnections proposed by Pitts *et al.* (1939).

BOOK REVIEWS AND NOTICES

ESSAYS IN BIOLOGY. In Honor of HERBERT M. EVANS. Written by his Friends. Pp. 687; many illus. Berkeley and Los Angeles: University of California Press, 1943. Price, $10.00.

AN examination of this memorial volume, written in honor of Dr. Herbert Evans (including a complete bibliography of his work and 48 essays contributed by his friends and associates) stimulates the reader with thoughts concerning the present status of the individual scientist in the ever widening field of experimental biology. One thinks of the scope of biological research, and that we are all experimental biologists. Thus, an essay "On the Growth of Deer Antlers" is found next to one on the "Heart in Myxedema," and Sigerist's "Impotence as a Result of Witchcraft" precedes H. P. Smith's discussion of the quantitative aspects of blood coagulation.

Then one is reminded of the high degree of specialization to which biology has evolved by the 3 papers dealing with the relation between minerals, Na and K, carbohydrate metabolism and the adrenals, which are written by Jane Russell, Evelyn Anderson, and Irvine McQuarrie.

One might well wonder to what extent an individual might cover such a wide field in the presence of competition to be expected from the highly specialized. A study of Evans' bibliography shows that he worked on problems in anatomy, physiology, nutrition, chemistry, biochemistry, and embryology. Of interest is the fact that he published 19 papers in the first decade of his career, and 22 in the single year of 1942. Tacit implication of far-reaching changes that have taken place is found in the fact that the former papers were published in 11 different journals, while the latter were carried by 9, only 1 of which is among the first list, and most of the 8 remaining were nonexistent at the beginning of Evans' researches.

Among the essays are a number of historical papers which are new and refreshing, in that they bring within reach of the reader information concerning which everyone could find quotations but few could actually read. One of these is a translation of Purkinje's "Contributions to the History of the Bird's Egg Previous to Incubation." Here is related that the distinguished scientist was not the first "to suffer the violent disturbance in a university circle when the reflected glimmer of established dignity began to fade in the light of a major luminary."

An article on the forgotten theorems of Carnot brings to light the false premises upon which the law of the conservation of energy was founded. Yet we must not forget that this law was the foundation upon which our knowledge of energy metabolism was based, which today has made it possible for war leaders to calculate the energy requirements of the soldiers in terms as accurate as those used to determine the gallons of gasoline demanded by the engines which drive the machines of modern warfare.

Although there might be few people who can read every essay critically, there is no question but that everyone can find in this volume a number of essays worthy of close attention. J. S.

ALLERGY, ANAPHYLAXIS AND IMMUNOTHERAPY. Basic Principles and Practice. By BRET RATNER, M.D., Clinical Professor of Pediatrics, New York University College of Medicine; Visiting Pediatrician and Director of Pediatrics, Sea View Hospital, etc. Pp. 824; 88 illus.; 56 tables. Baltimore, Md.: The Williams and Wilkins Company, 1943. Price, $8.50.

THERE is no phase of clinical medicine now untouched by the ever widening field of allergy at one time or another. Modern treatment of infectious dis-

eases is based more than ever before on the principles of immunology. The problems of immunotherapy are inseparably linked with those of allergy and no internist can afford to be ignorant of their basic principles.

Dr. Ratner has carried on extensive laboratory and clinical studies in this field and has produced a book of incalculable value. He indicates the insidious ways in which allergic sensitization may be acquired and points out the dangers of indiscriminate serum and sulfonamide therapy. The uses of vaccines, toxoids, blood transfusions, and blood substitutes, are also presented in minute detail. The text proceeds from descriptions of materials and methods of their preparation to the details of immunotherapy in the major disease entities. In its latter portion there is a complete discussion of allergy to immunotherapeutic agents which also includes the principles of allergy in general. The subject matter is well presented. The illustrations are complete and satisfactory. In short, it is a work which should prove invaluable to the internist in general, but particularly to the allergist and immunologist.

M. M.

HUMAN NEUROANATOMY. By OLIVER S. STRONG, Formerly Professor of Neurology and Neurohistology, College of Physicians and Surgeons, Columbia University, and ADOLPH ELWYN, Associate Professor of Neuroanatomy, College of Physicians and Surgeons, Columbia University. Pp. 417; 320 figures. Baltimore: Williams & Wilkins Company, 1943. Price, $6.00.

DESIGNED primarily for students, this text is sufficiently complete and detailed to obviate the student's need of any larger references and to be of value to many physicians. Neuroembryology, neurohistology, and the peripheral nervous system are discussed in the first 80 pages and are followed by a systematic description of the central nervous system, with pertinent data on functional changes, with "judicious repetition," and with frequent coördination of the new facts with those already learned by the student. Illustrations are abundant, well done, and interspersed with the text. Frequent usage of a photograph with an adjacent diagram of the identically same region adds to the clarity of presentation. This volume is well done, up to date, and equal, at least, to any in this field.

M. F.

TEXTBOOK OF ANATOMY AND PHYSIOLOGY FOR NURSES. By CARL C. FRANCIS, A.B., M.D., Senior Instructor in Anatomy, Department of Anatomy, Western Reserve University, Cleveland; G. CLINTON KNOWLTON, PH.D., Assistant Professor of Physiology, College of Medicine, State University of Iowa; and W. W. TUTTLE, PH.D., Professor of Physiology, College of Medicine, State University of Iowa. Pp. 586; 338 illus. (38 color plates). St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

THIS new anatomy and physiology textbook intended for student nurses is more compact than the usual text of this kind. It is clearly written and well illustrated with photographs, color plates, and pertinent descriptions.

The subject matter is arranged in units which are not wholly in accord with the pattern suggested in the 1937 *Curriculum Guide for Schools of Nursing.* Generally speaking, chapters follow one another in logical sequence with the exception of the chapter on "Nutrition and Metabolism" which may prove confusing to those students who have not yet studied the digestive system.

Superimposed photographs of exceptional clarity and many detailed illustrations make the sections on articulations, muscles, and nerves of especial value to both student and teacher of anatomy and physiology.

Despite occasional minor errors in terminology and labeling of diagrams which indicate the need for more careful editing, this Reviewer has found the book adequate as a text for teaching, and excellent as a reference book for student nurses. Suggestions which may improve its teaching merits are; summaries of the most important facts at the end of each system, and more practical applications of and references to the actual nursing situations which the student will encounter.

H. F.

PICTORIAL HANDBOOK OF FRACTURE TREATMENT. By EDWARD L. COMPERE, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School; Chairman, Department of Orthopædic Surgery, Wesley Memorial Hospital; Consulting Orthopædic Surgeon, Chicago Memorial Hospital; and SAM W. BANKS, M.D., Associate in Surgery, Northwestern University Medical School; Attending Orthopædic Surgeon, Chicago Memorial Hospital. Pp. 351; 171 figs. Chicago: Year Book Publishers, 1943. Price, $4.25.

THE entire field of fracture treatment is covered in an exceedingly brief, terse, and pithy style. Controversial points are strictly avoided, and only one method of treatment is described for each type of fracture. An abundance of small, lucid, straight-to-the-point drawings and roentgenographs assist in making this small volume useful to the general practitioner who is forced by necessity of location to treat fractures, and who often is obliged to learn the "simple facts" in some haste. M. F.

PAPERS FROM THE SECOND AMERICAN CONGRESS ON GENERAL SEMANTICS. Non-Aristotelian Methodology (Applied) for Sanity in Our Time. Compiled and Edited by M. KENDIG. Pp. 581. Chicago: Institute of General Semantics, 1943. Price, $5.00.

SINCE the publication in 1933 of Alfred Korzybski's "Science and Sanity: An Introduction to Non-Aristotelian Systems and General Semantics," which may be taken as launching the Semantics movement, this discipline has made steady if not conspicuous progress. The founding of the Institute of General Semantics in Chicago in 1938 and a General Congress has now been followed by the Second American Congress on the subject in July 1943; under the Presidency of Franklin Ebaugh, M.D., of the University of Colorado.

This stout volume includes over 80 papers divided into 2 books. The first and shorter, which deals with Non-Aristotelian Orientations and the Methodology with Related Subjects, presents, *inter alia*, a historical introduction by O. L. Reiser and general discussions by Korzybski and Adolf Meyer. The reader who is not familiar with the theory and terminology of General Semantics will find them briefly explained in Korzybski's 17-page paper (p. 93).

The lengthier Book 2, on Human Adjustment, is concerned with the newer approaches to such far-flung subjects as Neuropsychiatric Foundations, Medical Education and Practice, Physiotherapy, Stuttering, Vision, Dental Caries, Nutrition, Mental Hygiene, Marital Counseling, Pathology, behaviorism and so on. One might reasonably question how closely such subjects are related to Semantics and in fact examination shows that in many it either plays a small and unnecessary rôle or does not appear at all, the topic thus being treated as it would be at any professional meeting—and some not too well treated at that.

Semantics is basically concerned with language. The word, coined by Bréal in 1897 from the Greek, "significant" is used mostly in the sense of the meaning of words and their significance. One is not surprized, therefore, to find a number of papers on such topics as language, public speaking, movies, journalism, teaching of English, and so on. It is in such fields that Semantics can first bring practical results. Old Aristotle as usual comes in for some hard knocks, mostly undeserved; but he doubtless can take these and is glad to do so if knowledge is advanced thereby. Better knowledge of the true meanings of words and their significances, added to a conscientious use of this knowledge, would remove much unnecessary confusion in scientific and other discussions, much of the illegitimate and harmful effects of propaganda, advertising, broadcasting, and other evils peculiar to the present day. Shakespeare's mellifluous response to his own query "What's in a name?" (a "purr" Semanticism, incidentally) is much less valid than Socrates' axiom: "I have no objection to your giving names any significance that you please if you will only tell me what you mean by them."

Semantics, being necessarily a subject that deals in many abstractions and

tends to attract theorists and those who deal in or fall for "hot air," the pilots and well-wishers of the movement would do well to see that its more vocal followers keep their feet on the ground as well as Nature permits and that those wanting to ride on the bandwagon are not permitted to twist a valuable concept unsemantically to suit their selfish purposes. E. K.

DIAGNOSIS OF UTERINE CANCER BY THE VAGINAL SMEAR. By GEORGE N. PAPANICOLAOU, M.D., PH.D., Department of Anatomy, Cornell University Medical College, New York; and HERBERT F. TROUT, M.D., Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital. Pp. 46; 11 colored plates. New York: The Commonwealth Fund, 1943. Price, $5.00.

IN this monograph are embodied the results of routine vaginal smear examinations from 3014 women, most of whom were in the cancer-bearing age. It entails "probably between 7000 and 10,000" smears. Of the 179 patients found to have primary cancer of the uterus, 127 were from the cervix and 53 from the fundus. Of the 127 cervical lesions, failure to detect the malignant cells in the smears occurred 4 times; in the 53 fundic lesions it occurred 7 times. An analysis of these failures revealed that most cases were either post-irradiational or were patients with adenoma malignum. In several instances the authors suspected malignant disease before one or more biopsies confirmed it. The authors emphasize that the vaginal smear method is not recommended as a means of ultimate diagnosis, but to be confirmed by biopsy, since the evaluation of individual cells is a much more difficult task than the recognition of cancer in tissue preparations. In view of the surprisingly high accuracy of diagnoses of these men, the ease of obtaining smears and the relatively simple technical procedure combine to form a seemingly valuable diagnostic as well as follow-up method for the gynecologist and pathologist. It is also apparent that the use of this method is of value only in the hands of those thoroughly familiar and experienced in cytologic detail in isolated and clumped cells arising from an area so richly endowed with varying cell types. The text is devoted largely to describing the types of cells found in vaginal smears under various physiologic and pathologic conditions, and these are illustrated by excellent colored camera lucida drawings and microphotographs. M. T.

BORDERLANDS OF PSYCHIATRY. By STANLEY COBB, M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 166; 27 figs. Cambridge, Mass.: Harvard University Press, 1943. Price, $2.50.

IN this Fourth Harvard University Monograph in Medicine and Public Health, the author is concerned with a somewhat neglected 6½ million persons who are partially incapacitated. The chapter on "Body and Mind" with its 5 case histories shows the fallacy of the terms functional or organic, mental or physical, since "every symptom is both functional and organic." In the section on "Parallel Evolution of Speech, Vision and Intellect," it is asserted that at birth both cerebral hemispheres appear equipotential, but through inheritance the learning process tends to be unilateral; through the special senses symbolic meanings develop and these are correlated into language. "Speech and Language Defects" show that the former is probably "the most integrated and sensitive of the human functions. . . . it normally and abnormally is affected by many stimuli." Accordingly, the collaboration of different specialists is required to solve the problem of stammering. "Functions of the Frontal Area" suggest the undesirability of removing a portion of the brain, thereby rendering "the patient lazy and indiscriminating . . . . in order to make the patient happier." "The Anatomical Basis of Emotions" speaks of the hypothalamus not as a "center of emotion" of feeling, but as "a motor

way-station where emotion is integrated into behavior patterns . . . ." But emotion may "take place in a rudimentary way in the thalamus of man, and in a much more discriminative way in the cerebral cortex." In "Consciousness," the varying depths of sleep are studied through electrograms. Levels of wakefulness range from mania to stupor. It is suggested that later, consciousness may be described in terms of electrotonic activity. Concerning "Fits," the functional abnormalities of epilepsy are described as "*(1) changes in electrical potentials as seen in the electro-encephalogram; (2) changes in consciousness; (3) nervous discharge into smooth muscle, striated muscle, or glands, causing involuntary visceral or motor behavior.*" Psychoneurosis admittedly is a difficult condition to define and measure. It has been described as "a personality disorder severe enough to cause the patient to seek medical advice or be advised to seek help." There are estimated to be 2,500,000 psychoneurotics in the country. "Psychosomatics" is a new term but not a new condition. In 1907, Kreibich, a German, reported the induction of a blister on the skin through hypnosis. More extensive lesions have been induced and it is argued that such phenomena may probably occur in tissues less accessible to scrutiny. These disorders are said to be concerned largely with emotions, feelings, autonomic neurology, and related medical symptoms, including hysteria.

Though a book of such miscellaneous contents is one of essays rather than a monograph, with rare discrimination and skill, the author has painstakingly presented much illuminating material. N. Y.

CHEMICAL SPECTROSCOPY. By WALLACE R. BRODE, Professor of Chemistry, Ohio State University. Second Ed. Pp. 677; 1 colored plate; numerous illus., spectrum tables and charts. New York: John Wiley & Sons, Inc., 1945. Price, $7.50.

THIS edition of Brode's text follows the general plan of the first edition. Revision, except for the inclusion of spectrum tables with relative intensities of lines based upon the data of G. R. Harrison (M. I. T.), has not been extensive.

The text is well written, and provides a readable, useful summary of information upon various types of spectroscopic equipment. The spectrum tables and charts, wisely relegated to a separate section of the book, will be useful for reference.

The work is intended for the chemist and chemical student who desire to use spectroscopy as an analytical tool. While absorption spectra are perhaps adequately treated, this phase of the subject could have been somewhat expanded to render the book more useful to students of medicine and biology.

The general excellence of the text is such that the Reviewer regrets that such factors as "errors" and "limitations" of technique have not been adequately treated. From the standpoint of the student, it might have been preferable also to present in more critical detail the use of a small number of representative instruments, rather than to furnish a general account (as the author has done) of a large variety of equipment.

This text is recommended as a worthwhile work which provides a panoramic view of the field it covers. D. D.

THE BOY SEX OFFENDER AND HIS LATER CAREER. By LOUIS J. DOSHAY, M.D., Psychiatrist, Children's Courts, New York City; Formerly Senior Assistant Physician, Manhattan State Hospital, New York, and Assistant Specialist in Neuropsychiatry, U. S. Veterans Hospital, New York. Foreword by GEORGE W. HENRY, M.D. Pp. 206; 40 tables, 12 diagrams. New York: Grune & Stratton, Inc., 1943. Price, $3.50.

NOT knowing of any similar work, the author has sought to determine what bearing sexual delinquencies of boys ranging from 7 to 16 years, has had upon

their lives between the ages of 16 and 28. Feebleminded boys and all girls were excluded. While boys commit many non-sexual offenses, those of girls are usually sexual—"a different set of motivations and dynamics is involved." Two important groups were considered: those showing sexual offenses exclusively, and those delinquent in a mixed sense—thievery, truancy, etc., included. The commonest offenses were: "lewdness, voyeurism, excessive masturbation, exhibitism, fornication, assault, incest, active and passive perverted practices with juveniles or adults of the same sex." In the total of 256 subjects, delinquencies were shown as not due to disparity in ages of the parents. The finding of only 4% with glandular defects shows the fallacy in believing endocrine dysfunction a contributor to much criminality. Except for incest with sisters, "so-called good boys commit just as many violent sexual offenses as the confirmed delinquent, indicating that forecast and treatment ought not rest on the sex offense alone." Orthodox psychoanalysis is interdicted since "the long-drawn-out procedure and the inevitable emphasis on the original sex offense, is diametrically opposite to the needs of the case." Given appropriate court and clinic treatment, it is believed these delinquents tend to be cured automatically. This valuable and stimulating study includes much statistical matter.

N. Y.

THE RÔLE OF NUTRITIONAL DEFICIENCY IN NERVOUS AND MENTAL DISEASE. Vol. XXII. Proceedings of the Association, Dec. 19 and 20, 1941, New York. Editorial Board: STANLEY COBB, M.D., Chairman; EDWIN F. GILDEA, M.D., HARRY M. ZIMMERMAN, M.D. Pp. 215; 23 illus., 8 tables. Baltimore: Williams & Wilkins Company, 1943. Price, $4.00.

THIS most recent volume in the series annually issued by the Association for Research in Nervous and Mental Disease is considerably reduced in size, unquestionably due to the turning of the medical profession to problems of war. The contributions are divided into those from the fundamental sciences and those from clinical research.

Among the former is a concise review of the relationship of enzymes to nutritional deficiencies by C. A. Elvehjem. It is, of necessity rather technical, but sufficiently clear and elementary to plot the course this field has traversed in research, and to give the direction for further progress. H. E. Himwich presents the biochemical advances of recent years in the relationship of thiamin and nicotinic acid to cerebral metabolism. The pathology of the vitamin B group deficiencies by H. M. Zimmerman provides the high water mark of this volume. The material for this review is largely Dr. Zimmerman's personal work, and this symposium provided an opportunity to summarize, correlate and evaluate the pathologic changes of vitamin B group deficiencies as found in man with the changes produced experimentally in animals. A most informative review of the effects of vitamin E deprivation in various laboratory animals is presented by A. M. Pappenheimer. Other articles in the first portion of the volume are by Dr. Cowgill (principles of research in nutrition); Drs. Wolbach and Bessey (the mechanical relationship of vitamin A deficiency and the central nervous system in the immature animal); Ferrebee, Weissman, Parker and Owen (thiamin content of human tissue).

Outstanding contributions of clinical research are by Wilder and by Spies, Bradley, Rosenbaum and Knott, emphasizing the psychologic disturbances resulting from thiamin deficiency. These controlled studies demonstrate that the earliest evidences of thiamin deficiency are in the emotional sphere and that mental disturbances in pellagrous patients should be considered as probably partially composed of a thiamin deficient element and not completely attributed to niacin deficiency. A review of the mental and neurologic aspects of thiamin, niacin and pyridoxine deficiencies by W. H. Sebrell rounds out this phase of the problem.

In a review of multiple neuritis, M. B. Streuss again points out that thiamin deficiency is probably not the only factor in polyneuritic changes, and nutritional polyneuritis should be treated by other nutritional factors as well as

with thiamin. Other multiple neuritides are discussed and differentiated from nutritional polyneuritis. Other clinical contributions include an article on psychiatric syndromes caused by nutritional deficiency by Bowman and Wortis, which comprehends a discussion of delerium tremens, Korsakoff's syndrome and Wernicke's disease. Evidence is presented from blood pyruvate studies that the latter is definitely associated with thiamin deficiency.

In spite of these many important contributions, however, this volume is not up to the previous standards of the Society. H. S.

AIR-BORNE INFECTION. By DWIGHT O'HARA, M.D., Professor of Preventive Medicine, Tufts College Medical School; Visiting Physician, Boston City Hospital; Physician-in-Chief, Waltham Hospital. Pp. 114; several charts and tables. New York: The Commonwealth Fund, 1943. Price, $1.50.

THE author unveils an interesting sketch of the problem of air-borne infections as seen through the eyes of a student of preventive medicine. While not entirely ignoring the contact rôle of infection, Dr. O'Hara merely sidesteps the issue for he is interested mainly in the air-borne phases of such diseases as smallpox, diphtheria, the common cold, pneumonia, streptococcus infections, tuberculosis and others.

Since 1900 there has been a definite decrease in the mortality rates of such diseases. The author attempts to probe out the causes and presents his observations on the decline of air-borne infection.

Among his conclusions he states that the greatest contribution in the improvement of our respiratory health between 1918–1938 has been made by the hygienists and sanitarians in what he describes as a better "living standard." The author does not give entire credit to them, however, for he also discusses the rôle of accepted preventive measures, immunization, decreased virulence, advanced therapeutic measures, strengthened resistance and reduced concentration of atmospheric infection, as well as the isolation of infecting sources. Each and all have had a part in the rapid decrease of air-borne infections.

This book could be read to great advantage by every practitioner and public health officer, for it contains good discussions and observations of the truths underlying the decline of air-borne infections. F. E.

MEDICAL CLINICS OF NORTH AMERICA. Symposium on Physical Therapy, Mayo Clinic Number, July 1943. Pp. 317; many illus. Philadelphia: W. B. Saunders Company. Price, year $16.00.

THIS symposium includes 20 articles by members of the Staff of the Mayo Clinic and by medical officers of both services stationed there. The principles and techniques of physical medicine applicable to arthritis, vascular diseases, poliomyelitis (the Kenny treatment), backache and other problems are discussed for both hospital and ambulatory patients. Simple methods and devices for home use are stressed. The management of common war disabilities by physical and also occupational therapy are adequately considered. This issue is to be recommended because a careful attempt has been made to evaluate and present the best of the current methods in this field of ever-growing usefulness. R. H.

THE MICROSCOPE AND ITS USE. By FRANK J. MUÑOZ, Technical Microscope Consultant; in Collaboration with DR. HARRY A. CHARIPPER, Professor of Biology, New York University. Pp. 334; 122 figs. Brooklyn, N. Y.: Chemical Publishing Company, Inc., 1943. Price, $2.50.

THE book is preëminently "popular," and in effect consists of chapters which serve as introductions to the microscope (and its many accessories, such as lighting fixtures, mechanical stages, counting chambers, demonstration ocu-

lars, photomicrographic cameras, etc.), the metallurgic microscope, and the polarizing microscope. The authors go beyond the information usually contained in pamphlets provided by manufactures, and discuss rather technical subjects such as "numerical aperture," Kohler illumination, resolution, and so forth, in a simplified language, although adequate for those who will find this book of value. The glossary is helpful. A small bibliography introduces the reader to several valuable references.

The text will be useful as an introduction to the equipment available for fields in which the microscope is employed. E. W.

PRINCIPLES AND TECHNIQUES OF NURSING PROCEDURES. By SISTER MARY AGNITA CLAIRE DAY, St. Louis University School of Nursing. Pp. 574; 94 illus. St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

THIS book is a compilation of nursing practices as developed in St. Mary's Group of hospitals of St. Louis University. The text constitutes a good procedure book. The organization of material follows to some extent the plan set forth in the *Curriculum Guide for Schools of Nursing*. Each procedure is headed by a brief discussion of its underlying principles, indications and contraindications, and other factors which seem essential to understanding. The book eliminates unnecessary duplication of material which is discussed in detail in other courses. If the text is used only as a procedure book, it may prove satisfactory; however, more consideration should be given to the philosophy of education and the psychology of learning processes. There is a dearth of correlation between the principles and practices of nursing and their underlying sciences. Little import is given to the nurse as a teacher of hygiene and preventive medicine. The procedures, however, are simple and are adaptable to both home and hospital situations. N. Y.

AN INTRODUCTION TO CLINICAL PERIMETRY. By H. L. TRAQUAIR, M.D., R.F.R.C.S. (ED.), Ophthalmic Surgeon, Royal Infirmary, Edinburgh; Ophthalmic Surgeon, Charles Chalmers Hospital, Edinburgh; Oculist to the Edinburgh Municipal Hospitals; Lecturer on Diseases of the Eye, Edinburgh University. Fourth ed. Pp. 332; 245 illus.; 3 colored plates. London: Henry Kimptom, 1942. Price, $6.50.

TRAQUAIR continues the outstanding book on perimetry. A few illustrations have been added. There have been surprisingly few changes or additions to the text. War conditions have appreciably changed the format, in that the cover, binding and paper are inferior. On the other hand, the smaller size of the book makes for easier use. A. C.

VICTORIES OF ARMY MEDICINE. Scientific Accomplishments of the Medical Department of the United States Army. By EDGAR ERSKINE HUME, Colonel, Medical Corps, United States Army. Pp. 250; 42 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $3.00.

IN wartime days, when the medical effort of the whole country is so largely devoted, directly or indirectly, toward military medicine, it is both especially appropriate that this book should appear, and fortunate that it should come from the pen of such an experienced writer and distinguished physician as Colonel Hume. One's hopes are not disappointed. Walter Reed's demonstration of the mode of yellow fever transmission and Beaumont's contribution to knowledge of gastric digestion are so well known to everyone that they have been treated here with commendable brevity. But other less well known, important contributions of the United States Army Medical Department furnish the material for the bulk of the volume.

The 14 well-balanced chapters first sketch in 45 pages the course of the U. S. Army Medical Department since 1775. Then follow descriptions of "Three great American Medical Institutions" (the Army Medical Library and its Index Catalogue, the Army Medical Museum, the Army Medical School); Anthropology; Ornithology; the Army's gift to Surgery, and the Reed and Beaumont chapters. Changing to a chronologic approach, the advances during and between four war periods are described in as many chapters, the two final chapters disposing of various miscellaneous items.

As in any good history, the Reference section is copious and the Index adequate.

Colonel Hume has amply proved his thesis that United States Army medical officers have made their share of worthy contributions to medical science. The medical profession as a whole should certainly read this book and become better acquainted with the achievements of their Army Medical Department, while the thousands now on active service undoubtedly will want to know more about its distinguished past. E. K.

SYNOPSIS OF TROPICAL MEDICINE. By SIR PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P., Senior Physician to the Hospital for Tropical Diseases, Royal Albert Dock and Tilbury Hospitals; Consulting Physician in Tropical Diseases to the Dreadnought Seaman's Hospital, London; Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Medicine to the Admiralty and to the Royal Air Force; Lumleian Lecturer, Royal College of Physicians, 1941. Pp. 224; 5 plates. Baltimore: Williams & Wilkins Company, 1943. Price, $2.50.

THE author of this book is the well-known authority on tropical medicine who has so successfully edited the many editions of "Manson's Tropical Diseases." The text seems to be a condensed version of the larger volume, with contents rearranged into what strikes this Reviewer as a more logical sequence. To accomplish this degree of condensation and still maintain reasonable completeness, the author has resorted to telegraphic style, outlines and abbreviations wherever possible. The result is a pocket-size book containing the essential facts. It should have wide usefulness for many years. H. R.

REHABILITATION OF THE WAR INJURED. A Symposium. Edited by WILLIAM BROWN DOHERTY, M.D., and DAGOBERT D. RUNES, PH.D. Pp. 684; many illus. New York: Philosophical Library, Inc., 1943. Price, $10.00.

THE editors and publishers of this work have rendered an important service to the war effort by assembling in one volume the writings of outstanding authorities in many fields on subjects pertaining to rehabilitation of military casualties. The main sections cover Neurology and Psychiatry, Reconstructive and Plastic Surgery, Orthopedics, Physiotherapy, Occupational Therapy and Vocational Guidance, and Legal Aspects of Rehabilitation. The principal usefulness of this book will be to inform those engaged in planning for rehabilitation as to what can be accomplished by specialists in the several fields of medicine. No book of this length and covering so many fields could be adequate for the needs of the specialist himself, but such is not the editors' intent. The volume is specifically recommended to the personnel of the military departments of the armed services, particularly those of policy-making rank, so that they may judge for themselves as to the adequacy of the treatment being provided to war casualties for whom they are responsible.

One half of the 54 articles are provided with bibliographies of varying completeness. It is regrettable that the authors were not all required to provide complete bibliographies, because the value of the work would thereby have been greatly enhanced. J. L.

DICTIONARY OF BIOCHEMISTRY AND RELATED SUBJECTS. Editor-in-Chief, WILLIAM MARIAS MALISOFF, Professor of Bio-Chemistry at the Polytechnic Institute of Brooklyn. Pp. 579. New York: Philosophical Library, Inc., 1943. Price, $7.50.

THE Editor-in-Chief explains that "The dictionary contains a great deal of glossary material, and also a great deal of fairly lengthy authoritative discussion. It tried to maintain a balance between obsolescent, established and newly explored material. It is designed for readers of biochemical literature who might want the definition of terms used more than a decade ago as well as of terms just coined."

Forty-six collaborators have aided in compiling approximately 10,000 definitions of biochemical terms. Some 50 items receive from 1 to 17 pages of authoritative discussion—thus accounting for approximately one-half of the volume. Many of the articles are well documented with references.

Relatively few errors have been found, though some definitions appear inadequate. Some quotations have not been given with their proper content.

The Editor should be congratulated upon this attempt in designing a dictionary in this field. It should be very useful to the student of "biochemistry" and to workers in related fields. H. V.

MEDICO-LEGAL BLOOD GROUP DETERMINATION. Theory, Technique, Practice. By DAVID HARLEY, M.D., B.Sc., F.I.C., The Laboratories of the Inoculation Department, St. Mary's Hospital, London. Pp. 119; 13 figs.; 23 tables. London: William Heinemann. Distributors in U. S. A., Grune & Stratton, Inc., New York, 1943. Price, 12s 6d.

THE application of Blood Group determinations to forensic medicine constitutes an advance in scientific legal investigation. The lag in the acceptance by the courts in this country of blood group determinations as admissible evidence, and the lack of legislation authorizing the court to order such examinations make it particularly important that every possible means of spreading information on the subject among both legal and medical practitioners of all kinds be available. In this respect, we are far behind the medico-legal practice of many countries on the Continent, Russia and Japan.

In this volume, the theory of blood groups, their hereditary character, techniques for their determination in blood, and in stains of blood, saliva and semen, are discussed in detail. The possibilities and the limitations of the evidence to be obtained from such examinations are presented.

A number of cases are cited to demonstrate how evidence may be obtained from the examination of blood and of stains of various kinds. Such sections on the need for the test in the civil courts in the determination of non-paternity is excellent. E. W.

AN INTRODUCTION TO SOCIOLOGY AND SOCIAL PROBLEMS. By DEBORAH MACLURG JENSEN, Instructor in Sociology and Social Problems at the Schools of Nursing of St. Louis City Hospital and St. Luke's Hospital; Lecturer in Nursing Education, Washington University. Second ed. Pp. 420; 78 figs. St. Louis: C. V. Mosby Company, 1943. Price, $3.25.

LIMITED in scope to the needs of the student nurse, Mrs. Jensen's textbook introduces the more elementary concepts of sociology and presents social problems that the nurse is likely to encounter in our immediate culture.

The text has been arranged to coincide accurately with suggestions given in the *Curriculum Guide for Schools of Nursing* and has been revised to include social changes that may arise from the present war. Written with clarity and insight, it is keyed to the gait of the average nursing school student. Helpful features are arresting picture graphs, widely chosen bibliographies, and thought provoking questions for discussion at the end of each chapter.

It is the Reviewer's opinion that supplemented with references as suggested this would make an exceptionally good nursing text in sociology. H. F.

ROENTGENOGRAPHIC TECHNIQUE. By DAMON A. RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Missouri Pacific Hospital, and the Arkansas Children's Hospital, Little Rock. Third ed. Pp. 471; 201 engravings. Philadelphia: Lea & Febiger, 1943. Price, $5.50.

THIS text is filling an important field in radiology. Diagnostic radiology is undergoing many improvements and the author, through his revisions, has kept his text up to date and, therefore, keeps his readers informed. In this new edition, the author has revised the text thoroughly in the fields where there have been advances in roentgenographic technique. The paper is good, the print is easy to read, and the illustrations are excellent; throughout, the author has used negative illustrations. This is very important because many technicians have difficulty in transposing positive illustrations to what they see on the roentgenograms. The book should be in every department where radiology is done. E. P.

INJURIES OF SKULL, BRAIN AND SPINAL CORD. Edited by SAMUEL BROCK, M.D., New York University. Second ed. Pp. 616; 78 figs. Baltimore: Williams & Wilkins Company, 1943. Price, $7.00.

THIS symposium on injuries to the central nervous system edited by Dr. Brock contains relatively few changes from the first edition. Many chapters have been rewritten but little material has been added.

The precise details on the methods of administration and the place of sulfonamides in cases of open cranial trauma even now is not fully agreed upon; nevertheless, the data introduced into this new edition, on this most important subject, appears to be inadequate.

The outstanding difference from the first edition is the inclusion of a chapter on the electroencephalogram in cases of head trauma by Paul F. A. Hoefer. This chapter contains excellent observations both electroencephalographically and clinically on a large series of cases, presented in the form of many tables. The place and value of electroencephalography in cranial trauma however is not clearly presented. The article has more of the tone of a statistical report in a journal publication than a chapter in a text or reference volume.

An adequate discussion on the controversial subject of the treatment of closed cranial trauma is still lacking in this new edition. Certainly this subject deserves fuller consideration of the rationales guiding the many opposing views on therapy. Unfortunately the chapter on concussion and contusion of the brain was not revised and a consideration of the important work of Denny-Brown and Russell on the place of acceleration in the physiology of cerebral trauma—a milestone in this field—failed to be included.

This book remains, despite the above criticisms, the best on the subject and continues to be invaluable to the profession in the understanding and handling of central nervous system injuries, both medically and legally.

H. S.

NEW BOOKS

Clinical Diagnosis by Laboratory Examinations. By JOHN A. KOLMER, M.S., M.D., DR.P.H., SC.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry of Temple University; Director of the Research Institute of Cutaneous Medicine; Formerly Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania. Pp. 1239; 75 figs. New York and London: D. Appleton-Century Company, Inc., 1943. Price, $8.00.

Tifus Exanthemático. Etiología—Clínica—Profilaxis. By PROF. DR. G. CLAVERO and DR. F. PÉREZ GALLARDO. Prólogo del PROF. DR. J. A. PALANCA. Gráficas Afrodisio Aguado, S. A.—Bravo Murillo, 31., Madrid. 1941.

Barometric Pressure. Researches in Experimental Physiology. By PAUL BERT. Translated from the French by MARY ALICE HITCHCOCK, M.A., Formerly Professor of Romance Languages at the University of Akron; and FRED A. HITCHCOCK, PH.D., Associate Professor of Physiology at The Ohio State University. Pp. 1055; 23 tables; 89 figs. Columbus, Ohio: College Book Company, 1943. Price, $12.00.

A Clinical and Experimental Investigation of the Blood Cholesterol Content in Myxœdema and Other Conditions. By E. H. STOKES, M.B., CH.M. (SYDNEY), F.R.A.C.P., Senior Honorary Assistant Physician, Sydney Hospital; Tutor and Honorary Lecturer in Medicine, University of Sydney. Accepted as a thesis for admission to the degree of Doctor of Medicine in the University of Sydney. Pp. 121; 13 figs.; 12 tables. Sydney, Australia: Australasian Medical Publishing Company, Ltd., 1941. No price given.

Biomicroscopy of the Eye. Slit Lamp Microscopy of the Living Eye, Vol. 1. By M. L. BERLINER, M.D., Assistant Professor of Clinical Surgery (Ophthalmology), Cornell University Medical College; Associate Attending Surgeon, New York Hospital; Assistant Surgeon, New York Eye and Ear Infirmary; Instructor in Biomicroscopy, Post-Graduate School, New York Eye and Ear Infirmary; Senior Associate Attending Ophthalmologist, Beth Israel Hospital, New York. Pp. 709; 512 illus. (40 pages color plates). New York and London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1943. Price, $17.50.

Investigación del Virus Tifoexanthemático en las Ratas de España. By DR. G. CLAVERO and F. PÉREZ GALLARDO. Publicaciones de la Revista de Sanidad e Higiene Publica. May, 1943. Madrid.

La Prueba Intradérmica de Giroud en la Infección Tifoexanthemática. By G. CLAVERO and F. PÉREZ GALLARDO. Publicaciones de la Revista de Sanidad e Higiene Publica. December, 1942. Madrid.

Finger Prints, Palms and Soles. An Introduction to Dermatoglyphics. By HAROLD CUMMINS, PH.D., Professor of Microscopic Anatomy, Tulane University, School of Medicine; and CHARLES MIDLO, M.D., Associate Professor of Microscopic Anatomy, Tulane University (Formerly Assistant Professor of Anatomy, Louisiana State University). Pp. 309; 149 illus. Philadelphia: Blakiston Company, 1943. Price, $4.00.

Biological Symposia. Edited by JAQUES CATTELL, Editor of "The American Naturalist" and "American Men of Science." Vol. X. Frontiers in Cytochemistry. Pp. 334; several figs. Lancaster, Pa.: The Jaques Cattell Press, 1943. Price, $3.50.

The Biochemistry of Malignant Tumors. By KURT STERN, M.D., Formerly Research Associate of the University of Vienna, New York City; and ROBERT WILLHEIM, M.D., Professor, University of Philippines, Manila. Pp. 951. Brooklyn, N. Y.: Reference Press, 1943. Price, $12.00.

Urological Diseases of Pregnancy. By E. GRANVILLE CRABTREE, M.D., Urologist to the Boston Lying-In Hospital. With a signed chapter by GEORGE C. PRATHER, M.D., Assistant Urologist to the Boston Lying-In Hospital. Pp. 472; 158 figs., several in color. Baltimore: The Williams & Wilkins Company, 1942. Price, $5.00.

Electronic Interpretations of Organic Chemistry. By A. EDWARD REMICK, PH.D., Assistant Professor of Chemistry, Wayne University, Detroit. Pp. 474. New York: John Wiley & Sons, Inc., 1943. Price, $4.50.

A Surgeon's World. An Autobiography. By MAX THOREK, M.D. Pp. 410. Philadelphia and New York: J. B. Lippincott Company, 1943. Price, $3.75.

Physiological Psychology. By CLIFFORD T. MORGAN, Associate in Psychology, The Johns Hopkins University; Formerly Faculty Instructor in Psychology, Harvard University. Pp. 623; 176 figs. New York and London: McGraw-Hill Book Company, Inc., 1943. Price, $4.00.

NEW EDITIONS

An Introduction to Clinical Perimetry. By H. M. TRAQUAIR, M.D., F.R.C.S. (ED.), Ophthalmic Surgeon, Royal Infirmary, and Chalmers Hospital, Edinburgh; Oculist to the Edinburgh Municipal Hospital; Lecturer on Diseases of the Eye, Edinburgh University. With a Foreword by NORMAN M. DOTT, M.D., CH.B., F.R.C.S. (ED.). Fourth ed. Pp. 332; 245 illus., 3 colored plates. London: Henry Kimpton, 26 Bloomsbury Way, W. C. 1, 1942. Price, $6.50. (See review in this issue.)

Introduction to Physiological and Pathological Chemistry. By L. EARLE ARNOW, PH.G., B.S., PH.D., M.B., M.D., Director of Biochemical Research, Medical-Research Division, Sharp & Dohme, Inc., Glenolden, Pa.; Professor of Chemistry, Bryn Mawr College Summer School of Nursing, 1941–43; Formerly Assistant Professor of Physiological Chemistry, University of Minnesota Medical School, and Lecturer in Physiological Chemistry to Students enrolled in the University of Minnesota School of Nursing, Minneapolis. Introduction by KATHARINE J. DENSFORD, B.A., M.A., R.N., Director of the School of Nursing and Professor of Nursing, University of Minnesota. Second ed. Pp. 574; 142 figs, 31 tables. St. Louis: The C. V. Mosby Company, 1943. Price, $3.75.

Urine and Urinalysis. By LOUIS GERSHENFELD, P.D., PH.M., D.SC., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Second ed. Pp. 304; 42 figs. Philadelphia: Lea & Febiger, 1943. Price, $3.25.

Personal and Community Health. By C. E. TURNER, A.M., SC.D., DR.P.H., Professor of Public Health in the Massachusetts Institute of Technology; Formerly Associate Professor of Hygiene in the Tufts College Medical and Dental Schools; Sometime Member of the Administrative Board in the School of Public Health of Harvard University and the Massachusetts Institute of Technology. Seventh ed. Pp. 585; many figs., 4 colored plates. St. Louis: The C. V. Mosby Company, 1943. Price, $3.50.

A Textbook of Medicine. Edited by RUSSELL L. CECIL, A.B., M.D., SC.D., Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, New York Hospital; Visiting Physician, Bellevue Hospital, New York City. Associate Editor for "Diseases of the Nervous System;" and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Clinical Neurology, Cornell University Medical College; Attending Physician, New York Hospital; Visiting Physician in Charge, Neurological Service, Bellevue Hospital; Consulting Physician, New York Neurological Institute. Sixth ed. Pp. 1566; 193 figs. Philadelphia and London: W. B. Saunders Company, 1943. Price, $9.50.

Textbook of Physiology. By WILLIAM D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University); and W. W. TUTTLE, PH.D., Professor of Physiology, College of Medicine, State University of Iowa. Eighth ed. Pp. 728; 308 text illus., 3 color plates. St. Louis: The C. V. Mosby Company, 1943. Price, $4.75.

This book is sufficiently in demand to appear in new editions every few years consequently its form shows a gradual progress without violent changes. In this edition some changes have been made in presentation and many of the figures have been redrawn. Some of the newer knowledge is incorporated but the scope of the book, which is written for students with little background, does not justify the use of such material on a large scale. H. B.

China's Health Problems. By SZEMING SZE, General Secretary, Chinese Medical Association, Editor, Chinese Medical Journal. Pp. 60. Washington, D. C.: Chinese Medical Association (P. O. Box 6096), 1943. Price, $1.00.

Quantitative Pharmaceutical Chemistry. Containing Theory and Practice of Quantitative Analysis Applied to Pharmacy. By GLENN L. JENKINS, PH.D., Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota; and ANDREW G. DUMEZ, PH.D., Professor of Pharmacy and Dean of the School of Pharmacy, University of Maryland. Second ed., 6th impression. Pp. 466; 67 figs.; 69 tables. New York and London: McGraw-Hill Book Company, Inc., 1937.

CORRECTIONS

In the June 1943 issue of this Journal, the article by Dr. C. P. Rhoads, C.T., Klopp and J. C. Abels entitled "The Relationship Between Riboflavin Intake and Thiamin Excretion in Man," should have had as its title—"The Relationship Between Thiamin Intake and Riboflavin Excretion in Man."

In the article on The Present Status of Contrast Myelography iu the section "Radiology under the direction of Harry M. Weber, M.D., and David G. Pugh, M.D.," appearing in November issue, the author was wrongly given in the authors' manuscript as Dr. Weber instead of Dr. Pugh.

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We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.

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